CONDENSED PYRIDINE COMPOUND

This application is a divisional of co-pending Application No. 09/509,778, filed on March 31, 2000 and for which priority is claimed under 35 U.S.C. § 120. Application No. 09/509,778 is the national phase under 35 U.S.C. § 371 of PCT International Application No. PCT/JP98/04465 filed on October 2, 1998. The entire contents of each of the above-identified applications is hereby incorporated by reference. This application also claims priority under 35 U.S.C. § 119 to Application No. 9-284290 filed in Japan on October 2, 1997.

Field of the Invention

The present invention relates to a clinically useful medicament having a serotonin antagonism, in particular, that for treating, ameliorating and preventing spastic paralysis or central muscle relaxants for ameliorating myotonia.

Background of the Invention

Myotonia, which seriously restrains daily life, is induced by any of a number of factors or a combination thereof, for example, cervico-omo-brachial syndromes accompanying stiffness or pain in the neck, shoulder, arm, lumbar and dorsal skeletal muscles due to abnormal posture, fatigue, changes in the backbone with ageing etc., shoulder periarthritis accompanying inflammation in the tissues constituting the shoulder joint due to changes in the shoulder joint caused by trauma, etc., and spastic

paralysis wherein accelerated limb muscle tonus hinders voluntary movements.

In particular, spastic paralysis is a disease which accompanies limb muscle tonus, stiffening, walking difficulty, etc. and thus seriously restrains daily life.

Prior Art

It has been a practice to treat these diseases mainly with the use of medicaments. At the present stage, central muscle relaxants or peripheral muscle relaxants are administered to patients with these diseases.

Particular examples of used central muscle relaxants include Tolperisone hydrochloride, Baclofen, Tizanidine hydrochloride, Chlorzoxazone and Diazepam.

On the other hand, particular examples of used peripheral muscle relaxants include suxamethonium chloride, Pancuronium bromide and dantrolene sodium.

Central muscle relaxants act selectively on the central nervous system so as to relax muscles. Therefore, it is expected that those action on the upper center would exhibit a more potent muscle relaxant effect. However, there arise at the same time some problems including extrapyramidal symptoms and neurologic manifestations such as sleepiness, sluggishness and atony. Namely, there has been known hitherto no medicament capable of achieving well-balanced principal action and side effects.

Diazepam, which is inherently a minor tranquilizer, is efficacious against diseases accompanying mental symptoms such as anxiety, tension

and depression. However, its effect is too potent to merely ameliorate myotonia. With the use of diazepam, therefore, spastic paralysis can be relieved but there arise some problems such as dizziness.

On the other hand, suxamethonium chloride and Pancuronium bromide which are peripheral muscle relaxants are marketed exclusively as injections, which makes the chronic administration thereof difficult.

Dantrolene sodium is processed into injections and preparations for oral use and has a relatively potent muscle relaxant effect. However, it suffers from problems of having only a low margin of safety and frequently inducing muscular atony. Accordingly, it is difficult for those other than medical specialists to administer this medicine.

As discussed above, there has been known hitherto no medicaments for treating and ameliorating myotonia in spastic paralysis etc., which is clinically useful and has a high safety.

Disclosure of the Invention

Under these circumstances, the present inventors have conducted extensive studies to develop medicaments for treating, ameliorating and preventing spastic paralysis or central muscle relaxants which have a potent effect of ameliorating myotonia while sustaining a high safety and newly paid their attention to compounds having a serotonin antagonism. As a result, they have successfully found that a novel condensed pyridine compound represented by the following formula or a pharmacologically acceptable salt thereof has an excellent central muscle relaxant effect and a high safety and thus makes it possible to solve the above problems, thus completing the present invention.

Accordingly, the present invention aims at providing clinically useful novel medicaments which have well-balanced principal action and side effects and make it possible to overcome the problem encountering in the prior art that those acting on the upper center would exhibit a more potent muscle relaxant effect but at the same time suffer from some problems including extrapyramidal symptoms and neurologic manifestations such as sleepiness, sluggishness and weakness.

Because of the anti-serotonin effect, it is expected that the condensed pyridine compound of the present invention is moreover usable in preventing, treating and ameliorating depression, emotional disorders, schizophrenia, sleep disturbance, anxiety, spinal cord injury, thrombosis, hypertension, brain circulatory disturbances, peripheral circulatory disturbances, drug addiction, etc.

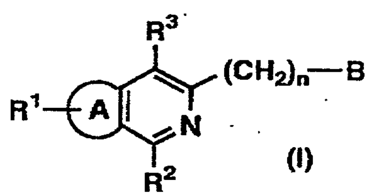
In addition to the condensed pyridine compound, the present invention provides medicinal composition which comprises a pharmaceutically effective dose of the condensed pyridine compound, its pharmaceutically acceptable salt or hydrates thereof and pharmaceutically acceptable carriers. Further, it provides an agent for treating, ameliorating or preventing diseases against which serotonin antagonism is efficacious, an agent for treating, ameliorating or preventing spastic paralysis and a muscle relaxant, which comprise the above-mentioned active ingredient.

Further, it provides a treating, ameliorating or

prophylactic agent comprising the above-mentioned effective ingredient for diseases for which the serotonin antagonism is efficacious or , a therapeutic, ameliorating and prophylactic agents of spastic paralysis and a muscle relaxation agent.

Furthermore, it provides a method for treating diseases against which the serotonin antagonism is efficacious or spastic paralysis, or ameliorating myotonia, which comprising the step of administering a pharmacologically effective dose of the condensed pyridine compound, its pharmacologically acceptable salt or hydrates thereof to a patient. Additionally, it provides the use of the effective ingredient for producing the above-mentioned medicaments.

Herein, the condensed pyridine compound (I) of the present invention is represented by the following formula:

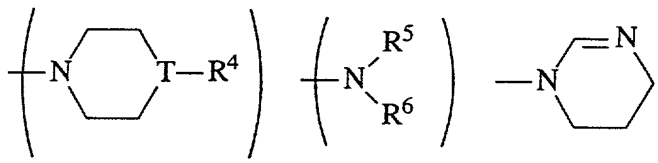


(I)

wherein, ring A represents benzene ring, pyridine ring, thiophene ring or furan ring;

R^1 represents hydrogen atom, halogen atom, a lower alkyl group or a lower alkoxyl group;

R^2 represents 4-morpholinyl group, 1-imidazolyl group, 1-lower alkyl homopiperazin-4-yl group or any one selected from the groups represented by the following formulae:



(wherein, T represents nitrogen atom or methine group;

R^3 represents hydrogen atom, halogen atom, a lower alkyl group or a lower alkoxyl group;

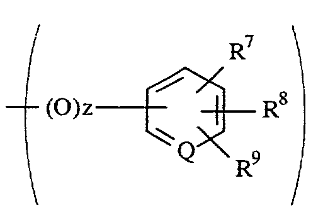
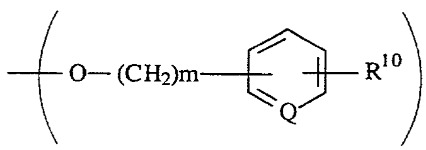
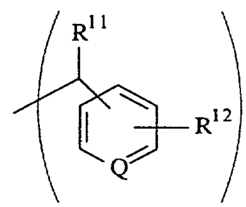
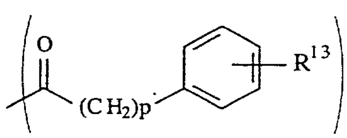
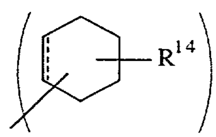
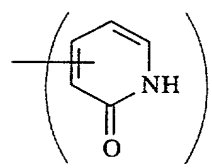
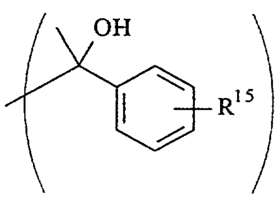
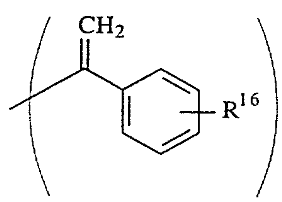
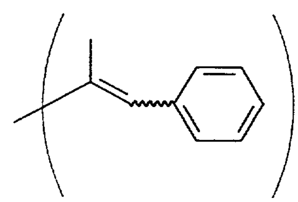
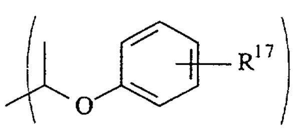
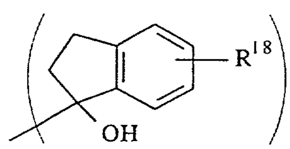
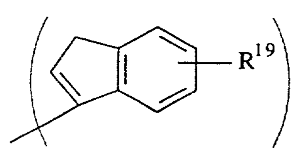
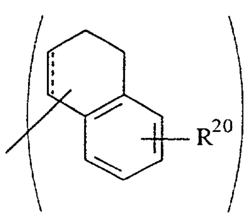
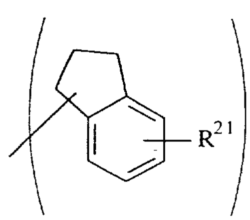
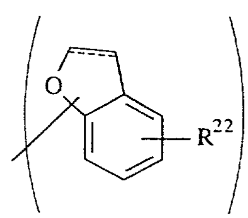
R^4 represents hydrogen atom, a lower alkyl group, a hydroxy lower alkyl group, a halogenated lower alkyl group, a lower cycloalkyl group, an aryl group, an aralkyl group, 1-piperidyl group, an alkenyl group, a cyano lower alkyl group, a carbamoyl lower alkyl group, a lower acyl group, an aromatic acyl group, a lower alkoxyl carbonyl group, an aryloxycarbonyl group or an aralkyloxycarbonyl group;

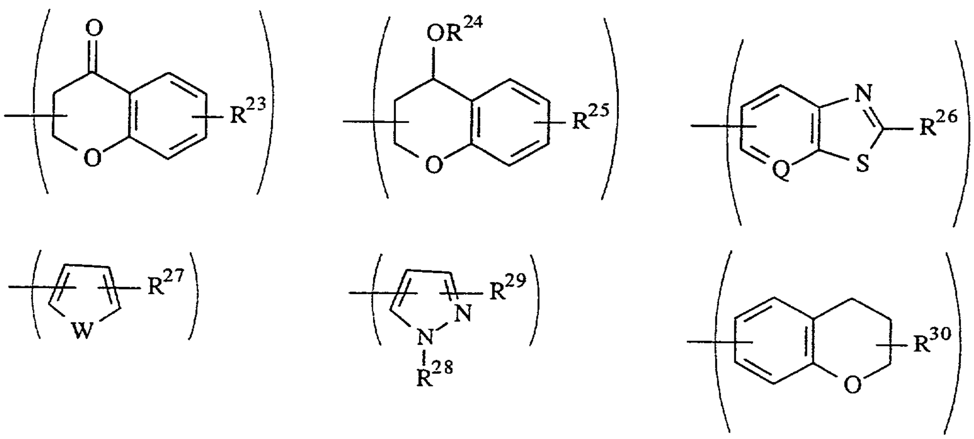
R^5 and R^6 are the same as or different from each other and each represents hydrogen atom, a lower alkyl group, a di lower alkyl aminoalkyl group, an optionally substituted heteroaryl lower alkyl group);

n represents 0 or an integer of 1 to 6; and

B represents an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted aralkyloxy group, an aryl(hydroxy)alkyl group, an aromatic acyl amino group, an arylsulfonylamino group, a lower alkoxyl arylsulfonylamino group, a hydroxy lower alkoxyl styryl group, a lower alkoxyl aryloxy group, 4-phenylpiperidin-1-yl group, 4-pyridylpiperidin-1-yl group, an optionally substituted arylalkenyl group, an optionally substituted

arylalkynyl group, an optionally substituted heteroarylalkenyl group, an optionally substituted heteroarylalkynyl group, an aromatic acyl alkynyl group, an optionally N-substituted amino lower alkyl group, an optionally substituted arylamino group, an optionally substituted aralkylamino group or any one selected from the groups represented by the following formulae:



(wherein z represents 0 or 1;

Q represents nitrogen atom or methine group;

R^7, R^8 and R^9 are the same as or different from each other and each represents hydrogen atom, halogen atom, hydroxyl group, a lower alkyl group, a lower alkenyl group, a lower alkynyl group, a lower alkoxyl group, a lower thioalkoxyl group, a hydroxy lower thioalkoxyl group, an arylthio group, a heteroarylthio group, a heteroaryl(hydroxy)alkyl group, a halogenated lower alkyl group, a hydroxy lower alkyl group, a dihydroxy lower alkyl group, a halogenated (hydroxy) lower alkyl group, a hydroxyalkenyl group, a hydroxyalkynyl group, a hydroxy lower cycloalkenyl group, a lower alkoxy(hydroxy)alkyl group, a lower alkoxy(hydroxy)alkoxy group, a lower alkoxyalkyl group, a lower alkoxyalkoxy group, a lower thioalkoxyalkoxy group, a lower alkylsulfonylalkoxy group, a hydroxy lower alkoxy group, a dihydroxy lower alkoxy group, a hydroxy lower alkylalkoxy group, a hydroxyimino lower alkyl group, a lower cycloalkyl (hydroxy) alkyl group, an aralkyl group, a hydroxyaralkyl group, cyano group, a cyano lower alkyl group, amide group (carbamoyl group),

an N-lower alkylamide group, an N-lower cycloalkylamide group, an N,N-di lower alkylamide group, an N-hydroxy lower alkylamide group, an N-hydroxy lower alkyl-N-lower alkylamide group, an N-arylamide group, cyclic aminocarbonyl group, carbamoyl group, an N-lower alkyl carbamoyl group, an N,N-di lower alkyl carbamoyl group, aminosulfonyl group, cyclic aminosulfonyl group, an N-lower alkylaminosulfonyl group, an N-lower cycloalkylaminosulfonyl group, an N,N-di lower alkylaminosulfonyl group, an N-hydroxy lower alkylaminosulfonyl group, an N-lower alkoxyalkylaminosulfonyl group, an N-halogenated lower alkylsulfonyl group, pyrrolidinylsulfonyl group, a lower alkylsulfonylaminoalkyl group, an N-lower alkylaminosulfonylalkyl group, an N,N-di lower alkylaminosulfonylalkyl group, a lower acyl group, a lower acylalkyl group, a lower cycloalkyl(hydroxy)methyl group, tetrahydropyranyl group, hydroxytetrahydropyranyl group, a hydroxy lower alkyltetrahydropyranyl group, a lower acylaminoalkyl group, (thiazol-2-yl)hydroxymethyl group, di(thiazol-2-yl)hydroxymethyl group, a lower alkylsulfonyl group, a lower alkoxyalkylsulfonyl group, a hydroxy lower alkylsulfonyl group, a lower alkylsulfonylalkyl group, an N-lower alkylamidealkyl group, an aryl group, an aralkyl group, a heteroaryl group, a heteroaryl lower alkyl group, a heteroaryl lower alkoxy group, a heteroarylsulfonyl group, 4-morpholinylsulfonyl group, 4-oxythiomorpholinylsulfonyl group, 4-dioxythiomorpholinylsulfonyl group, 4-

morpholinylsulfonyl group, a hydroxy lower cycloalkyl group, a hydroxy lower cycloalkyloxy group, a hydroxycycloalkenyl group, a halogenatedhydroxy lower alkyl group, 4-hydroxypiperidyl group, a 4-lower alkoxypiperidyl group, an ω,ω-lower alkylenedioxyalkyl group, an ω,ω-lower alkylenedioxyalkoxy group, a lower cycloalkylhydroxymethyl group, an aryloxy group, an arylaminosulfonyl group, amino group, a lower alkylamino group, a di lower alkylamino group, a hydroxy lower alkylamino group, a lower acylamino group, a hydroxy lower acylamino group, a lower alkylsulfonylamino group, a pyridyl lower alkoxy group, a lower alkylpyridylalkoxy group, a lower alkoxyhydroxyalkoxy group, a lower thioalkoxyalkoxy group, a lower alkylsulfonylalkoxy group, an N-lower alkylcarbamoyl group, an N,N-di lower alkylcarbamoyl group, an N-hydroxy lower alkylcarbamoyl group, an N-hydroxy lower alkyl-N-lower alkylcarbamoyl group, a halogenated lower alkoxy group, a cyano lower alkoxy group, a hydroxy lower cycloalkoxy group, trifluoromethyl group, trifluoromethoxy group, an amino lower alkoxy group, an N-lower alkyl aminoalkoxy group, an N,N-di lower alkylaminoalkoxy group, a lower acylalkoxy group, a lower acylaminoalkoxy group, a (1,3-dioxolanyl) lower alkyl group, a (1,3-dioxolanyl) lower alkoxyl group, an amide lower alkoxyl group, a 4-(hydroxyalkyl)tetrahydropyran-4-yl group, 2,3-dihydrobenzofuranyl group, a 2-hydroxy-2-alkyl-2,3-dihydrobenzofuranyl group, indanonyl group, hydroxyindanyl group, an imidazolyl lower alkoxyl group, succinimide group or

2-oxazolidon-3-yl group;

furthermore, R^7 represents hydrogen atom, while R^8 and R^9 form cyclopentanone ring, hydroxycyclopentane ring, a hydroxyalkylcyclopentane ring, cyclohexanone ring, hydroxycyclohexane ring, a hydroxyalkylcyclohexane ring, 2-hydroxymethyl-2-methylcyclopentanone ring, 1,2-ethylenedioxy ring or methylenedioxy ring;

m or p represents 0 or an integer of 1 to 6;

R^{10}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{25}, R^{27} and R^{29} independently represent hydrogen atom, halogen atom, hydroxyl group, a lower alkyl group, a lower alkoxy group, a hydroxy lower alkyl group, a hydroxy lower alkoxy group or tetrahydropyranyl group;

R^{11} represents hydrogen atom, halogen atom, hydroxy group, a lower alkyl group or a lower alkoxy group;

R^{24} represents hydrogen atom or a lower alkyl group;

R^{26} represents hydrogen atom or a hydroxy lower alkyl group;

R^{28} represents hydrogen atom or a lower alkyl group;

R^{30} represents hydrogen atom, a lower alkyl group, a lower alkoxy group, a hydroxy lower alkyl group or a hydroxy lower alkoxy group;

W represents sulfur atom or oxygen atom;

the bond represented by the following formula:

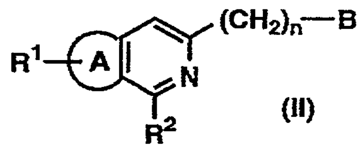
$$- - - - -$$

represents a single or double bond; and

the bond represented by the following formula:

represents trans or cis bond.).

Among these condensed pyridine compounds, the condensed pyridine compound (II) represented by the following formula is more preferable:

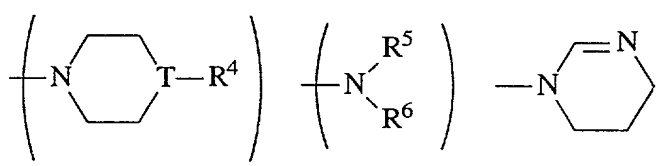


(II)

wherein, ring A represents benzene ring, thiophene ring or furan ring;

R^1 represents hydrogen atom, halogen atom, a lower alkyl group or a lower alkoxy group;

R^2 represents 4-morpholinyl group, 1-imidazolyl group, a 1-lower alkylhomopiperazin-4-yl group or any one selected from the groups represented by the following formulae:



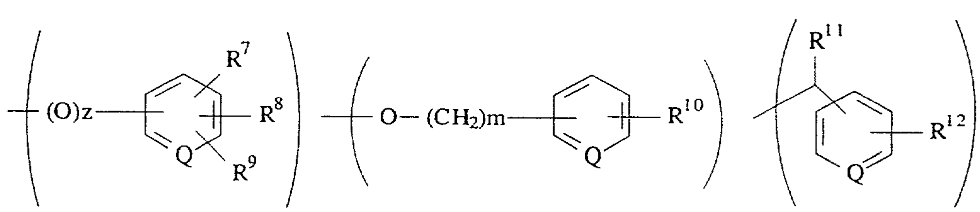
(wherein, T represents nitrogen atom or methine group;

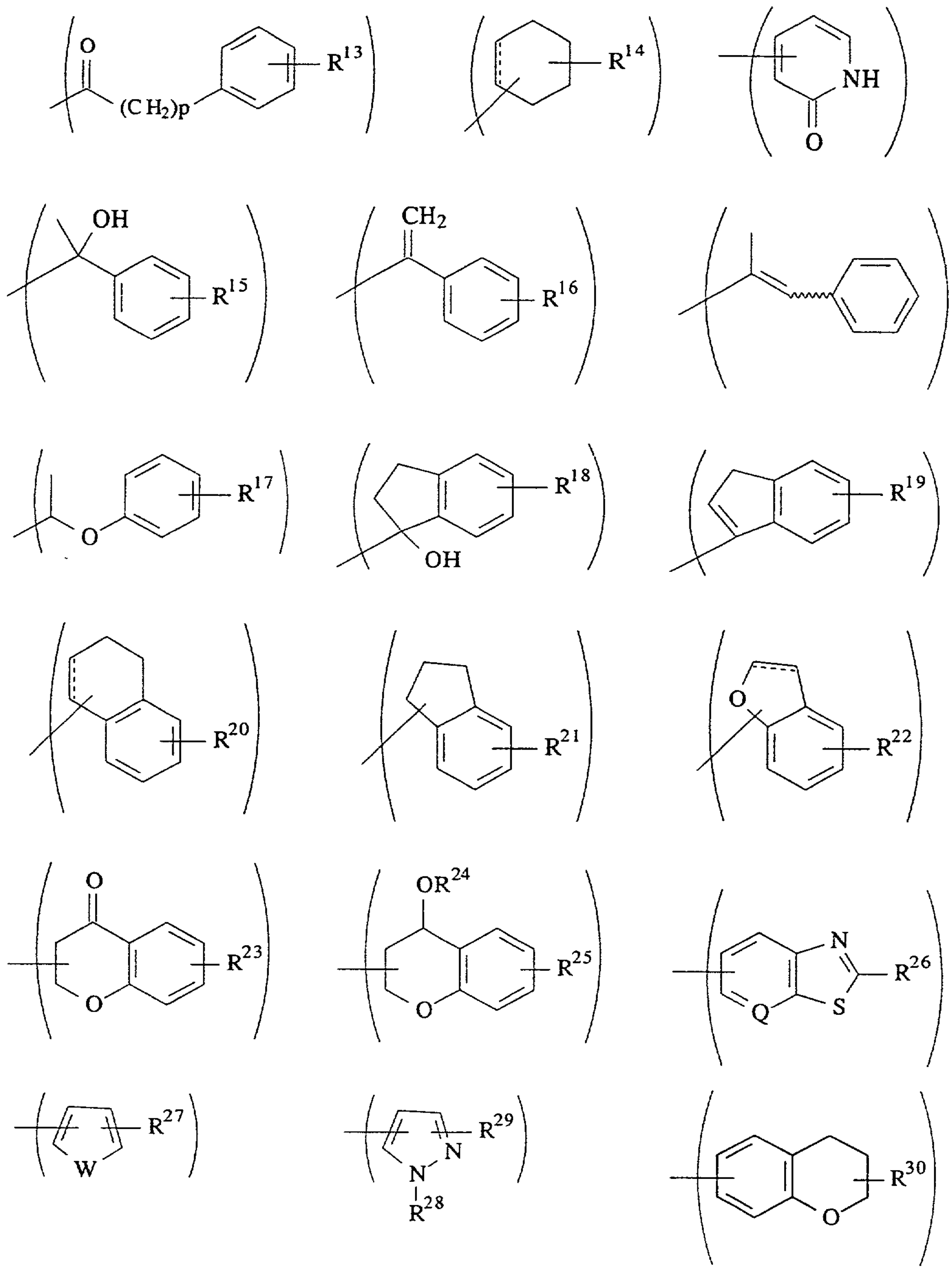
R^4 represents hydrogen atom, a lower alkyl group, a hydroxy lower alkyl group, a halogenated lower alkyl group, a lower cycloalkyl group, an aryl group, an aralkyl group, 1-piperidyl group, an alkenyl group, a cyano lower alkyl group, a carbamoyl lower alkyl group, a lower acyl group, an aromatic acyl group, a lower alkoxy carbonyl group, an aryloxycarbonyl group or an aralkyloxycarbonyl group; and

R^5 and R^6 are the same as or different from each other and each represents hydrogen atom, a lower alkyl group, a di lower alkylaminoalkyl group, an optionally substituted heteroaryl lower alkyl group.);

n represents 0 or an integer of 1 to 6; and

B represents an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted aralkyloxy group, an aryl(hydroxy)alkyl group, an aromaticacylamino group, an arylsulfonylamino group, a lower alkoxyarylsulfonylamino group, a hydroxy lower alkoxystyryl group, a lower alkoxyaryloxy group, 4-phenylpiperidin-1-yl group, 4-pyridylpiperidin-1-yl group, an optionally substituted arylalkenyl group, an optionally substituted arylalkynyl group, an optionally substituted heteroarylalkenyl group, an optionally substituted heteroarylalkynyl group, an aromaticacylalkynyl group, an optionally N-substituted amino lower alkyl group, an optionally substituted arylamino group, an optionally substituted aralkylamino group or any one selected from the groups represented by the following formulae:





(wherein, z represents 0 or 1;

Q represents nitrogen atom or methine group;

R^7, R^8 and R^9 are the same as or different from each other and each represents hydrogen atom, halogen atom, hydroxy group, a lower alkyl group, a lower alkenyl group, a lower alkynyl group,

a lower alkoxy group, a lower thioalkoxy group, a hydroxy lower thioalkoxy group, an arylthio group, a heteroarylthio group, a heteroaryl(hydroxy)alkyl group, a halogenated lower alkyl group, a hydroxy lower alkyl group, a dihydroxy lower alkyl group, a halogenated(hydroxy) lower alkyl group, a hydroxyalkenyl group, a hydroxyalkynyl group, a hydroxy lower cycloalkenyl group, a lower alkoxy(hydroxy)alkyl group, a lower alkoxy(hydroxy)alkoxy group, a lower alkoxyalkyl group, a lower alkoxyalkoxy group, a lower thioalkoxyalkoxy group, a lower alkyl sulfonylalkoxy group, a hydroxy lower alkoxy group, a dihydroxy lower alkoxy group, a hydroxy lower alkylalkoxy group, a hydroxyimino lower alkyl group, a lower cycloalkyl (hydroxy)alkyl group, an aralkyl group, a hydroxyaralkyl group, cyano group, a cyano lower alkyl group, amide group (carbamoyl group), an N-lower alkyl amide group, an N-lower cycloalkyl amide group, an N,N-di lower alkyl amide group, an N-hydroxy lower alkyl amide group, an N-hydroxy lower alkyl-N-lower alkyl amide group, an N-arylamide group, a cyclic amino carbonyl group, carbamoyl group, an N-lower alkyl carbamoyl group, an N,N-di-lower alkyl carbamoyl group, aminosulfonyl group, a cyclic amino sulfonyl group, an N-lower alkyl aminosulfonyl group, an N-lower cycloalkylaminosulfonyl group, an N,N-di lower alkyl aminosulfonyl group, an N-hydroxy lower alkylaminosulfonyl group, an N-lower alkoxyalkylaminosulfonyl group, an N-halogenated lower alkylsulfonyl group, pyrrolidinylsulfonyl group, a lower alkylsulfonylaminoalkyl group, an N-lower

alkylaminosulfonylalkyl group, an N,N-di lower alkylaminosulfonylalkyl group, a lower acyl group, a lower acylalkyl group, a lower cycloalkyl(hydroxy)methyl group, tetrahydropyranyl group, hydroxytetrahydropyranyl group, a hydroxy lower alkyltetrahydropyranyl group, a lower acylaminoalkyl group, (thiazol-2-yl)hydroxymethyl group, di(thiazol-2-yl)hydroxymethyl group, a lower alkylsulfonyl group, a lower alkoxyalkylsulfonyl group, a hydroxy lower alkyl sulfonyl group, a lower alkyl sulfonylalkyl group, an N-lower alkyl amidealkyl group, an aryl group, an aralkyl group, a heteroaryl group, a heteroaryl lower alkyl group, a heteroaryl lower alkoxy group, a heteroarylsulfonyl group, 4-morpholinylsulfonyl group, 4-oxythiomorpholinylsulfonyl group, 4-dioxythiomorpholinylsulfonyl group, 4-morpholinylsulfonyl group, a hydroxy lower cycloalkyl group, a hydroxy lower cycloalkyloxy group, a hydroxycycloalkenyl group, a halogenated hydroxy lower alkyl group, 4-hydroxypiperidyl group, a 4-lower alkoxy piperidyl group, an ω,ω-lower alkylene dioxyalkyl group, an ω,ω-lower alkylene dioxyalkoxy group, a lower cycloalkyl hydroxymethyl group, an aryloxy group, an arylaminosulfonyl group, amino group, a lower alkylamino group, a di lower alkylamino group, a hydroxy lower alkylamino group, a lower acylamino group, a hydroxy lower acylamino group, a lower alkylsulfonylamino group, a pyridyl lower alkoxy group, a lower alkylpyridylalkoxy group, a lower alkoxyhydroxyalkoxy group, a lower thioalkoxyalkoxy group, a

lower alkylsulfonylalkoxy group, an N-lower alkylcarbamoyl group, an N,N-di lower alkylcarbamoyl group, an N-hydroxy lower alkylcarbamoyl group, an N-hydroxy lower alkyl-N-lower alkylcarbamoyl group, a halogenated lower alkoxy group, a cyano lower alkoxy group, a hydroxy lower cycloalkoxy group, trifluoromethyl group, trifluoromethoxy group, an amino lower alkoxy group, an N-lower alkyl aminoalkoxy group, an N,N-di lower alkylaminoalkoxy group, a lower acylalkoxy group, a lower acylaminoalkoxy group, a (1,3-dioxolanyl) lower alkyl group, a (1,3-dioxolanyl) lower alkoxy group, an amide lower alkoxy group, a 4-(hydroxyalkyl)tetrahydropyran-4-yl group, 2,3-dihydrobenzofuranyl group, a 2-hydroxy-2-alkyl-2,3-dihydrobenzofuranyl group, indanonyl group, hydroxyindanyl group, an imidazolyl lower alkoxy group, succinimide group or 2-oxazolidon-3-yl group;

furthermore, R^7 represents hydrogen atom, while R^8 and R^9 may form cyclopentanone ring, hydroxycyclopentane ring, a hydroxyalkylcyclopentane ring, cyclohexanone ring, hydroxycyclohexane ring, a hydroxyalkylcyclohexane ring, 2-hydroxymethyl-2-methylcyclopentanone ring, 1,2-ethylenedioxy ring or methylenedioxy ring;

m or p represents 0 or an integer of 1 to 6;

R^{10}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{25}, R^{27} and R^{29} independently represent hydrogen atom, halogen atom, hydroxy group, a lower alkyl group, a lower alkoxy group, a hydroxy lower alkyl group, a hydroxy lower alkoxy group or

tetrahydropyranyl group;

the concrete examples of the heteroaryl group include 4-morpholinyl group, 2,6-dimethyl-4-morpholinyl group, 4-thiomorpholinyl group, 4-oxythiomorpholinyl group, 4-dioxythiomorpholinyl group, 1,3-dioxanyl group, 1,4-dioxanyl group, tetrahydrofuranyl group, dihydropyranyl group, 4,4-ethylenedioxypiperidin-1-yl group, 4-hydroxypiperidin-1-yl group, 4-methoxypiperidin-1-yl group, 4-acetylpiperazin-1-yl group, a 4-hydroxy lower alkyl piperidin-1-yl group and the like;

the concrete examples of the heteroaryl lower alkyl group include 4-morpholinylmethyl group, 4-thiomorpholinylmethyl group, a (tetrahydropyran-4-yl) lower alkyl group, pyridylmethyl group and the like;

R^{11} represents hydrogen atom, halogen atom, hydroxy group, a lower alkyl group or a lower alkoxy group;

R^{24} represents hydrogen atom or a lower alkyl group;

R^{26} represents hydrogen atom or a hydroxy lower alkyl group;

R^{28} represents hydrogen atom or a lower alkyl group;

R^{30} represents hydrogen atom, a lower alkyl group, a lower alkoxy group, a hydroxy lower alkyl group or a hydroxy lower alkoxy group;

W represents sulfur atom or oxygen atom;

the bond represented by the following formula:

$$\underline{\text{- - - - -}}$$

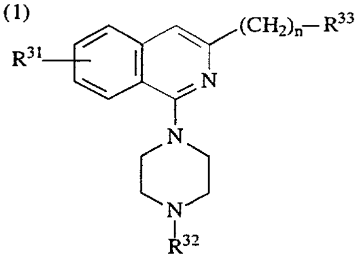
represents a single or double bond; and

the bond represented by the following formula:

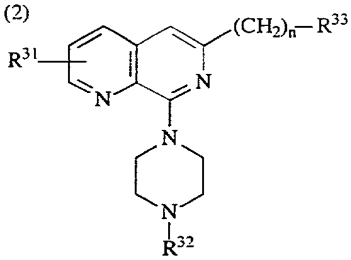
represents trans or cis bond.).

More specifically, the condensed pyridine compound of the present invention preferably include the condensed pyridine compounds represented by the following formulae:

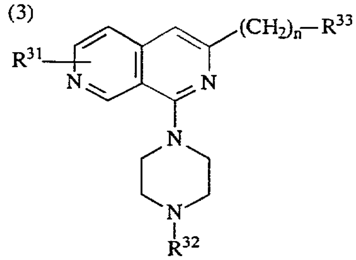
(1)



(2)



(3)



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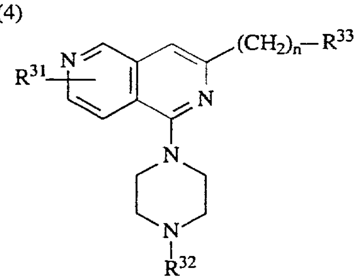

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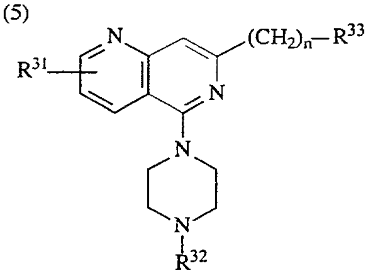

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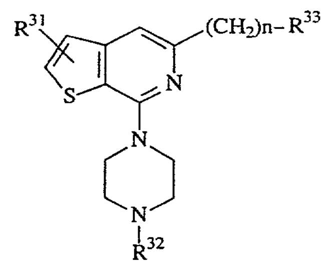

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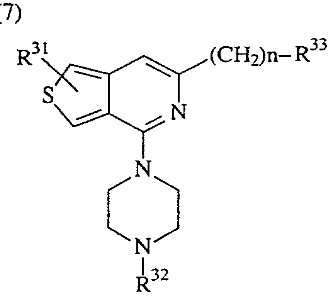

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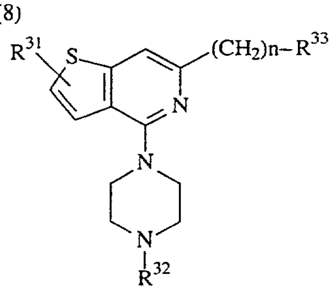

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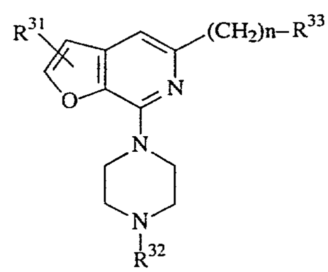

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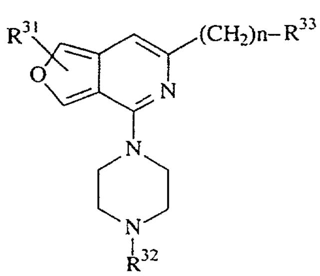

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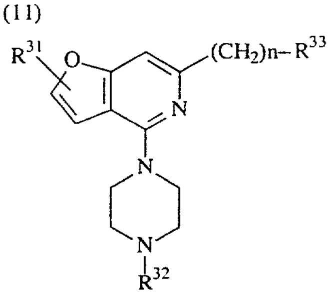


wherein, R^{31} has the same meaning as that of the above R^1, R^{32} has the same meaning as that of the above R^2 and R^{33} has the same meaning as that of the above B, respectively.

More specifically, the condensed pyridine compound of the present invention preferably includes the following ones:

(1) 3-(4-benzyloxybutyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(2) 1-(1-methylpiperazin-4-yl)-3-(4-methoxyphenyl)isoquinoline,

(3) 1-(1-methylpiperazin-4-yl)-3-[4-(2-hydroxyethoxy)phenyl]isoquinoline,

(4) 1-(4-ethylpiperazin-1-yl)-3-(4-trifluoromethylphenyl)isoquinoline,

(5) 1-(4-ethylpiperazin-1-yl)-3-[4-(1-fluoropropyl)phenyl]isoquinoline,

(6) 1-(4-ethylpiperazin-1-yl)-3-(2-hydroxyphenyl)isoquinoline,

(7) 1-(4-ethylpiperazin-1-yl)-3-(4-hydroxyphenyl)isoquinoline,

(8) 1-(4-ethylpiperazin-1-yl)-3-(2-methoxyphenyl)isoquinoline,

(9) 1-(4-ethylpiperazin-1-yl)-3-(3-methoxyphenyl)isoquinoline,

(10) 1-(4-ethylpiperazin-1-yl)-3-(4-methoxyphenyl)isoquinoline,

(11) 3-(2,3-dimethoxyphenyl)-1-(4-ethylpiperazin-1-

yl)isoquinoline,

(12) 3-(2,4-dimethoxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(13) 3-(2,5-dimethoxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(14) 3-(3,4-dimethoxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(15) 3-(3,5-dimethoxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(16) 1-(4-ethylpiperazin-1-yl)-3-(2,4,5-trimethoxyphenyl)isoquinoline,

(17) 1-(4-ethylpiperazin-1-yl)-3-(4-hydroxymethylphenyl)isoquinoline,

(18) 3-[2-(2-hydroxyethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(19) 1-(4-ethylpiperazin-1-yl)-3-[4-(1-hydroxypropyl)phenyl]isoquinoline,

(20) 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxypropyl)phenyl]isoquinoline,

(21) 1-(4-ethylpiperazin-1-yl)-3-[4-(1-hydroxybutyl)phenyl]isoquinoline,

(22) 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxybutyl)phenyl]isoquinoline,

(23) 3-[4-(4-hydroxybutyl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(24) 3-[4-(1,3-dihydroxypropyl)phenyl]-1-(4-ethylpiperazin-

1-yl)isoquinoline,

(25) 3-[4-(1,3-dihydroxy-3-methylbutyl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(26) 3-[4-(3-hydroxy-1-methoxybutyl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(27) 1-(1-ethylpiperazin-4-yl)-3-[4-(3-hydroxy-1-fluoropropyl)phenyl]isoquinoline,

(28) 1-(4-ethylpiperazin-1-yl)-3-[4-(4-hydroxymethyl-3-fluoro)phenyl]isoquinoline,

(29) 1-(4-ethylpiperazin-1-yl)-3-[3-fluoro-4-(1-hydroxypropyl)phenyl]isoquinoline,

(30) 3-[3-chloro-4-(3-hydroxypropyl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(31) 3-[3-carboxamide-4-(3-hydroxypropyl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(32) 3-[3-cyano-4-(3-hydroxypropyl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(33) 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxypropyl)-3-methoxyphenyl]isoquinoline,

(34) 3-[3-(3-hydroxypropyl)-4-methoxyphenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(35) 3-[3-(4-hydroxybutyl)-4-methoxyphenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(36) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxyethoxy)phenyl]isoquinoline,

(37) 3-[3,4-(2-dihydroxyethoxy)phenyl]-1-(4-ethylpiperazin-

1-yl)isoquinoline,

(38) 3-[3,5-(2-dihydroxyethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(39) 3-[3-chloro-4-(2-hydroxyethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(40) 3-[3-methyl-4-(2-hydroxyethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(41) 3-[3-isopropyl-4-(2-hydroxyethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(42) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-methoxyethoxy)phenyl]isoquinoline,

(43) 3-[3,4-(2-dimethoxyethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(44) 3-[4-(2-hydroxyethoxy)methylphenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(45) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-fluoroethoxy)phenyl]isoquinoline,

(46) 3-(3,4-methylenedioxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(47) 1-(1-ethylpiperazin-4-yl)-3-(4-acetonyloxyphenyl)isoquinoline,

(48) 3-[4-(3-aminopropoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(49) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-dimethylaminoethoxy)phenyl]isoquinoline,

(50) 3-[4-(3-acetamidepropoxy)phenyl]-1-(4-ethylpiperazin-

1-yl)isoquinoline,

(51) 3-(4-cyanomethoxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(52) 3-[4-(2-cyanoethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(53) 3-[4-(3-cyanopropoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(54) 3-[4-(3-methylthiopropoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(55) 3-[4-(3-methylsulfonpropoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(56) 3-{4-[2-(1-imidazonyl)ethoxy]phenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline,

(57) 3-{4-[3-(4-pyridyl)propoxy]phenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline,

(58) 3-{4-[2-(2-methylpyridin-5-yl)ethoxy]phenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline,

(59) 1-(1-ethylpiperazin-4-yl)-3-[4-(N-ethylcarbamyl)phenyl]isoquinoline,

(60) (Z)-1-(4-ethylpiperazin-1-yl)-3-(4-hydroxyiminomethylphenyl)isoquinoline,

(61) (E)-1-(4-ethylpiperazin-1-yl)-3-(4-hydroxyiminomethylphenyl)isoquinoline,

(62) 3-(4-cyanophenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(63) 1-(4-ethylpiperazin-1-yl)-3-(4-N-

propylaminocarbonylphenyl)isoquinoline,

(64) 3-[4-(4-hydroxy-1-cyclohexen-1-yl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(65) 3-(4-aminophenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(66) 3-[4-(N,N-dimethylamino)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(67) 3-[4-(2-hydroxyethyl)aminophenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(68) 3-(4-acetamidephenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(69) 3-(4-ethylcarbonylaminophenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(70) 3-(4-propylcarbonylaminophenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(71) 3-(4-ethylsulfonylaminophenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(72) 3-(4-propylsulfonylaminophenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(73) 3-(4-butylsulfonylaminophenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(74) 3-(4-sulfonamidephenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(75) 3-[(4-morpholinyl)sulfonylphenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(76) 3-[(4-thiomorpholinyl)sulfonylphenyl]-1-(4-

ethylpiperazin-1-yl)isoquinoline,

(77) 3-[(1,1-dioxythiomorpholinyl)sulfonylphenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(78) 3-(4-ethylsulfonylaminomethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(79) 3-(4-ethylsulfonylaminoethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(80) 3-(4-ethylaminosulfonylmethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(81) 3-(4-propylaminosulfonylmethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(82) 3-[4-(N,N-diethylamino)sulfonylmethylphenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(83) 3-[4-(tetrahydropyran-4-yl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(84) 3-[4-(5,6-dihydro-2H-pyran-4-yl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(85) 3-(4-ethylcarbonylaminomethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(86) 3-(4-propylcarbonylaminomethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(87) 3-(4-ethylaminocarbonylmethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(88) 3-(4-propylaminocarbonylmethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(89) 3-(4-butylaminocarbonylmethylphenyl)-1-(4-

ethylpiperazin-1-yl)isoquinoline,

(90) 3-(4-methylsulfonylmethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(91) 3-(3-chloro-4-ethylsulfonylaminomethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(92) 3-(3-chloro-4-propylsulfonylaminomethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(93) 3-(4-morpholinylmethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(94) 3-(4-thiomorpholinylmethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(95) 3-[4-(3-oxazolidinone)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(96) 3-[4-(4,4-ethylenedioxypiperidin-1-yl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(97) 1-(4-ethylpiperazin-1-yl)-3-[4-(4-hydroxypiperidin-1-yl)phenyl]isoquinoline,

(98) 1-(4-ethylpiperazin-1-yl)-3-[4-(4-methoxypiperidin-1-yl)phenyl]isoquinoline,

(99) 3-[2-(4-acetylpiperazin-1-yl)pyridin-5-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(100) 3-[4-(4-acetylpiperazin-1-yl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(101) 3-(2-methoxybenzyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(102) 3-[α-methyl-(4-methoxybenzyl)]-1-(4-ethylpiperazin-

1-yl)isoquinoline,

(103) 3-[α-hydroxy-(2-methoxybenzyl)]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(104) 3-[α-hydroxy-(4-methoxybenzyl)]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(105) 3-[α-methyl-α-hydroxy-(4-methoxybenzyl)]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(106) 1-(1-ethylpiperazin-4-yl)-3-(4-methoxyphenethyl)isoquinoline,

(107) 1-(1-ethylpiperazin-4-yl)-3-[2-(2-hydroxyethoxy)phenethyl]isoquinoline,

(108) 1-(1-ethylpiperazin-4-yl)-3-[3-(2-hydroxyethoxy)phenethyl]isoquinoline,

(109) 1-(1-ethylpiperazin-4-yl)-3-[4-(2-hydroxyethoxy)phenethyl]isoquinoline,

(110) 1-(1-ethylpiperazin-4-yl)-3-{3-[2-(2-hydroxyethoxy)phenyl]propyl}isoquinoline,

(111) 3-(2-methoxyphenylcarbonyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(112) 3-(4-methoxyphenylcarbonyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(113) 3-(4-methoxyindan-1-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(114) 3-(6-methoxyindan-1-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(115) 3-[4-(2-hydroxyethoxy)indan-1-yl)-1-(4-

ethylpiperazin-1-yl)isoquinoline,

(116) 3-(8-methoxy-1,2-dihydronaphthalen-4-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(117) 3-(7-methoxy-1,2-dihydronaphthalen-4-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(118) 3-(6-methoxy-1,2-dihydronaphthalen-4-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(119) 3-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(120) 3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(121) 3-(7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(122) 3-(3-hydroxymethylchroman-6-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(123) 1-(4-ethylpiperazin-1-yl)-3-(2-pyridyl)isoquinoline,

(124) 1-(1-ethylpiperazin-4-yl)-3-[5-(2-hydroxyethoxy)pyridin-2-yl]isoquinoline,

(125) 1-(1-ethylpiperazin-4-yl)-3-[2-(2-hydroxyethoxy)pyridin-5-yl]isoquinoline,

(126) 1-(1-ethylpiperazin-4-yl)-3-[2-(2-methoxyethoxy)pyridin-5-yl]isoquinoline,

(127) 1-(1-ethylpiperazin-4-yl)-3-[5-(2-methoxyethoxy)pyridin-2-yl]isoquinoline,

(128) 3-(2-propylcarbonylaminopyridin-5-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(129) 3-[(2-methylsulfonylpyridin)-5-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(130) 3-[(2-ethylsulfonylpyridin)-5-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(131) 1-(1-ethylpiperazin-4-yl)-3-(2-butylpyridin-5-yl)isoquinoline,

(132) 1-(1-ethylpiperazin-4-yl)-3-[5-(3-fluoropropyl)pyridin-2-yl)isoquinoline,

(133) 1-(1-ethylpiperazin-4-yl)-3-[2-(3-fluoropropyl)pyridin-5-yl]isoquinoline,

(134) 1-(1-ethylpiperazin-4-yl)-3-[5-(3-hydroxypropyl)pyridin-2-yl]isoquinoline,

(135) 1-(1-ethylpiperazin-4-yl)-3-[2-(3-hydroxypropyl)pyridin-5-yl]isoquinoline,

(136) 1-(1-ethylpiperazin-4-yl)-3-[2-(3-hydroxybutyl)pyridin-5-yl]isoquinoline,

(137) 1-(1-ethylpiperazin-4-yl)-3-[2-(4-hydroxybutyl)pyridin-5-yl]isoquinoline,

(138) 1-(1-ethylpiperazin-4-yl)-3-[2-(3-hydroxy-3-methylbutyl)pyridin-5-yl]isoquinoline,

(139) 1-(1-ethylpiperazin-4-yl)-3-[2-(3-methoxypropyl)pyridin-5-yl]isoquinoline,

(140) 1-(1-ethylpiperazin-4-yl)-3-[3-(3-methoxypropyl)pyridin-5-yl]isoquinoline,

(141) 1-(1-ethylpiperazin-4-yl)-3-[5-(3-methoxypropyl)pyridin-2-yl]isoquinoline,

(142) 1-(1-ethylpiperazin-4-yl)-3-[2-(3-ethoxypropyl)pyridin-5-yl]isoquinoline,

(143) 1-(1-ethylpiperazin-4-yl)-3-[2-[3-(2-propoxy)propyl]pyridin-5-yl]isoquinoline,

(144) 1-(1-ethylpiperazin-4-yl)-3-[2-(3-methoxybutyl)pyridin-5-yl]isoquinoline,

(145) 1-(1-ethylpiperazin-4-yl)-3-{2-[2-(2-hydroxy-2-cyclohexyl)ethynyl]pyridin-4-yl}isoquinoline,

(146) 1-(1-ethylpiperazin-4-yl)-3-[2-(1-butyn-1-yl)pyridin-5-yl]isoquinoline,

(147) 1-(4-ethylpiperazin-1-yl)-3-[2-(morpholin-4-yl)pyridin-5-yl]isoquinoline,

(148) 1-(4-ethylpiperazin-1-yl)-3-[5-(morpholin-4-yl)pyridin-2-yl]isoquinoline,

(149) 3-[2-(2,6-dimethylmorpholin-4-yl)pyridin-5-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(150) 1-(4-ethylpiperazin-1-yl)-3-[2-(thiomorpholin-4-yl)pyridin-5-yl]isoquinoline,

(151) 1-(4-ethylpiperazin-1-yl)-3-[2-(S-oxythiomorpholin-4-yl)pyridin-5-yl]isoquinoline,

(152) 1-(4-ethylpiperazin-1-yl)-3-[2-(4-hydroxypiperidin-1-yl)pyridin-5-yl]isoquinoline,

(153) 1-(4-ethylpiperazin-1-yl)-3-[2-(4-methoxypiperidin-1-yl)pyridin-5-yl]isoquinoline,

(154) 1-(4-ethylpiperazin-1-yl)-3-[2-(4-hydroxymethylpiperidin-1-yl)pyridin-5-yl]isoquinoline,

(155) 3-[2-(5,6-dihydro-2H-pyran-4-yl)pyridin-5-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(156) 3-[2-(tetrahydropyran-4-yl)pyridin-5-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(157) 3-[4-[3-(3-pyridyl)propoxy]phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(158) 1-(1-ethylpiperazin-4-yl)-3-(1-phenylpiperazin-4-yl)isoquinoline,

(159) 1-(1-ethylpiperazin-4-yl)-3-[1-(2-pyridyl)piperazin-4-yl]isoquinoline,

(160) 3-[4-(4-morpholinyl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(161) 1-(1-ethylpiperazin-4-yl)-3-(2-hydroxymethylthiophen-4-yl)isoquinoline,

(162) 1-(1-ethylpiperazin-4-yl)-3-(2-hydroxymethylthiophen-5-yl)isoquinoline,

(163) 1-(1-ethylpiperazin-4-yl)-3-[2-(2-hydroxyethyl)thiophen-5-yl]isoquinoline,

(164) 1-(1-ethylpiperazin-4-yl)-3-[2-(1-hydroxypropyl)thiophen-4-yl]isoquinoline,

(165) 1-(1-ethylpiperazin-4-yl)-3-[2-(1-hydroxypropyl)thiophen-5-yl)isoquinoline,

(166) 3-[2-(tetrahydropyran-4-yl)thiophen-5-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(167) 1-(1-ethylpiperazin-4-yl)-3-[4-methyl-5-(2-hydroxyethyl)thiazol-2-yl]isoquinoline,

(168) 1-(1-ethylpiperazin-4-yl)-3-(2-hydroxymethylthiazol-5-yl)isoquinoline,

(169) 1-(1-ethylpiperazin-4-yl)-3-[1-(2-hydroxyethyl)pyrazol-3-yl]isoquinoline,

(170) 1-(1-ethylpiperazin-4-yl)-3-[(1-hydroxypropyl)thiazol-5-yl]isoquinoline,

(171) 1-(1-ethylpiperazin-4-yl)-3-[2-(3-hydroxypropyl)thiazol-5-yl]isoquinoline,

(172) 1-(1-ethylpiperazin-4-yl)-3-[2-(3-methoxypropyl)thiazol-5-yl]isoquinoline,

(173) 1-(1-ethylpiperazin-4-yl)-3-[2-(4-morpholinyl)thiazol-5-yl]isoquinoline,

(174) 3-(2-propylcarbonylaminopyrimidin-5-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(175) 3-[2-(5,6-dihydro-2H-pyran-4-yl)thiophen-4-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(176) 3-[2-(5,6-dihydro-2H-pyran-4-yl)thiophen-5-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(177) 1-(1-ethylpiperazin-4-yl)-3-(phenylethynyl)isoquinoline,

(178) 1-(1-ethylpiperazin-4-yl)-3-(4-methoxyphenyl)ethynylisoquinoline,

(179) 1-(1-ethylpiperazin-4-yl)-3-(2-pyridyl)ethynylisoquinoline,

(180) 3-[3-(4-morpholinyl)-1-propynyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(181) 1-(1-ethylpiperazin-4-yl)-3-(3-phenyl-1-propynyl)isoquinoline,

(182) 1-(1-ethylpiperazin-4-yl)-3-(4-phenyl-1-butynyl)isoquinoline,

(183) 1-(1-ethylpiperazin-4-yl)-3-[4-(2-hydroxyethoxy)phenylethynyl]isoquinoline,

(184) 1-(1-ethylpiperazin-4-yl)-3-benzoylethynylisoquinoline,

(185) 1-(1-ethylpiperazin-4-yl)-3-(2,4-dimethoxyphenylethynyl)isoquinoline,

(186) 1-(1-ethylpiperazin-4-yl)-3-[3-(3-methoxypropyl)-5-pyridyl]ethynylisoquinoline,

(187) 1-(1-ethylpiperazin-4-yl)-3-[2-(2-hydroxyethoxy)phenyl]ethynylisoquinoline,

(188) 1-(1-ethylpiperazin-4-yl)-3-[3-(2-hydroxyethoxy)-2-pyridyl]ethynylisoquinoline,

(189) 1-(1-ethylpiperazin-4-yl)-3-(trans-2-phenylethenyl)isoquinoline,

(190) 1-(1-ethylpiperazin-4-yl)-3-[trans-2-(4-methoxyphenyl)ethenyl]isoquinoline,

(191) 1-(1-ethylpiperazin-4-yl)-3-[cis-2-(4-methoxyphenyl)ethenyl]isoquinoline,

(192) 1-(1-ethylpiperazin-4-yl)-3-(cis-1-methyl-2-phenylethenyl)isoquinoline,

(193) 1-(1-ethylpiperazin-4-yl)-3-(trans-1-methyl-2-phenylethenyl)isoquinoline,

(194) 1-(1-ethylpiperazin-4-yl)-3-[trans-2-(2-hydroxyethoxyphenyl)ethenyl]isoquinoline,

(195) 1-(1-ethylpiperazin-4-yl)-3-[trans-2-(2-methoxyphenyl)ethenyl]isoquinoline,

(196) 1-(1-ethylpiperazin-4-yl)-3-(trans-2-methyl-2-phenylethen-1-yl)isoquinoline,

(197) 1-(1-ethylpiperazin-4-yl)-3-[trans-2-(2-fluorophenyl)ethenyl]isoquinoline,

(198) 1-(1-ethylpiperazin-4-yl)-3-[(E)-4-(2-hydroxyethoxy)styryl]isoquinoline,

(199) 1-(1-ethylpiperazin-4-yl)-3-{trans-2-[3-(2-hydroxyethoxy)phenyl]ethenyl}isoquinoline,

(200) 3-{(E)-2-[2-(4-morpholinyl)pyridin-5-yl]ethenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline,

(201) 3-[(E)-2-(4-methylsulfonylphenyl)ethenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(202) 3-[(E)-2-(2-methylsulfonylphenyl)ethenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(203) 3-[(E)-2-(4-methylsulfonylmethylphenyl)ethenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(204) 3-{(E)-2-[3-(4-morpholinyl)phenyl]ethenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline,

(205) 3-{(E)-2-[4-(4-morpholinyl)phenyl]ethenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline,

(206) 3-{(E)-2-methyl-2-[4-(4-morpholinyl)phenyl]ethenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline,

(207) 3-{(E)-2-methyl-2-[3-(4-morpholinyl)phenyl]ethenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline,

(208) 3-[(E)-2-methoxymethyl-2-phenylethenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(209) 1-(1-ethylpiperazin-4-yl)-3-[trans-2-(2-pyridyl)ethenyl]isoquinoline,

(210) 1-(1-ethylpiperazin-4-yl)-3-[trans-2-(4-pyridyl)ethenyl]isoquinoline,

(211) 1-(1-ethylpiperazin-4-yl)-3-[3-(2-methoxy)phenyl-2-propenyl]isoquinoline,

(212) 1-(1-ethylpiperazin-4-yl)-3-[3-(2-hydroxyethoxy)phenyl-1-propenyl]isoquinoline,

(213) 3-{(E)-2-[2-(4-morpholinyl)pyridin-5-yl]ethenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline,

(214) 3-{(E)-2-[3-(4-morpholinyl)pyridazin-6-yl]ethenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline,

(215) 3-{(E)-2-[4-(4-morpholinyl)pyrimidin-6-yl]ethenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline,

(216) 3-{(E)-2-[2-(4-morpholinyl)pyrazin-6-yl]ethenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline,

(217) 3-[1-(4-methoxyphenyl)ethenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(218) 1-(1-ethylpiperazin-4-yl)-N-phenyl-3-isoquinolinecarboxamide,

(219) 1-(1-ethylpiperazin-4-yl)-3-(4-methoxyanilinomethyl)isoquinoline,

(220) 1-(1-ethylpiperazin-4-yl)-3-(4-methoxybenzylamino)isoquinoline,

(221) 1-(1-ethylpiperazin-4-yl)-4-methoxy-3-(4-methoxyphenyl)isoquinoline,

(222) 1-(1-ethylpiperazin-4-yl)-5-methyl-3-(4-methoxyphenyl)isoquinoline,

(223) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxyethoxy)phenyl]-6-fluoroisoquinoline,

(224) 1-(1-ethylpiperazin-4-yl)-6-fluoro-3-(4-methoxyphenyl)isoquinoline,

(225) 1-(1-ethylpiperazin-4-yl)-6-methyl-3-(4-methoxyphenyl)isoquinoline,

(226) 1-(4-ethylpiperazin-1-yl)-6-methoxy-3-(4-trifluoromethylphenyl)isoquinoline,

(227) 1-(4-ethylpiperazin-1-yl)-6-methoxy-3-(4-methoxyphenyl)isoquinoline,

(228) 1-(1-ethylpiperazin-4-yl)-7-methyl-3-(4-methoxyphenyl)isoquinoline,

(229) 1-(4-ethylpiperazin-1-yl)-7-fluoro-3-(4-methoxyphenyl)isoquinoline,

(230) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxyethoxy)phenyl]-7-fluoroisoquinoline,

(231) 1-(4-ethylpiperazin-1-yl)-7-methoxy-3-phenylisoquinoline,

(232) 1-(4-ethylpiperazin-1-yl)-7-methoxy-3-(2-methoxyphenyl)isoquinoline,

(233) 1-(1-ethylpiperazin-4-yl)-8-fluoro-3-(4-methoxyphenyl)isoquinoline,

(234) 1-(1-ethylpiperazin-4-yl)-8-fluoro-3-[4-(2-hydroxyethoxy)phenyl]isoquinoline,

(235) 1-(1-ethylpiperazin-4-yl)-8-methoxy-3-(4-methoxyphenyl)isoquinoline,

(236) 1-(1-propylpiperazin-4-yl)-3-(4-methoxyphenyl)isoquinoline,

(237) 1-(1-propylpiperazin-4-yl)-3-[4-(2-hydroxyethoxy)phenyl]isoquinoline,

(238) 1-(1-isopropylpiperazin-4-yl)-3-(4-methoxyphenyl)isoquinoline,

(239) 1-(1-cyclopropylpiperazin-4-yl)-3-(4-methoxyphenyl)isoquinoline,

(240) 1-(1-allylpiperazin-4-yl)-3-(4-methoxyphenyl)isoquinoline,

(241) 1-[1-(2-fluoroethyl)piperazin-4-yl]-3-(4-methoxyphenyl)isoquinoline,

(242) 1-[4-(2-hydroxyethyl)piperazin-1-yl]-3-(4-methoxyphenyl)isoquinoline,

(243) 3-(4-ethylsulfonylaminomethylphenyl)-1-[4-(2-hydroxyethyl)piperazin-1-yl]isoquinoline,

(244) 8-(4-ethylpiperazin-1-yl)-6-(4-methoxyphenyl)pyrido[2,3-c]pyridine,

(245) 8-(1-ethylpiperazin-4-yl)-6-[4-(2-hydroxyethoxy)phenyl]-1,7-naphthyridine,

(246) 8-(1-ethylpiperazin-4-yl)-6-{4-[(S)-2-hydroxypropoxy]phenyl}-1,7-naphthyridine,

(247) 8-(1-ethylpiperazin-4-yl)-6-[4-(3-hydroxypropyl)phenyl]-1,7-naphthyridine,

(248) 8-(1-ethylpiperazin-4-yl)-6-[4-(3-hydroxybutyl)phenyl]-1,7-naphthyridine,

(249) 8-(1-ethylpiperazin-4-yl)-6-[4-(3-hydroxy-1-fluoropropyl)phenyl]-1,7-naphthyridine,

(250) 8-(1-ethylpiperazin-4-yl)-6-[4-(2-hydroxy-2-methylpropoxy)phenyl]-1,7-naphthyridine,

(251) 1-(1-ethylpiperazin-4-yl)-3-(4-methoxyphenyl)-2,6-naphthyridine,

(252) 5-(1-ethylpiperazin-4-yl)-7-(4-methoxyphenyl)-1,6-naphthyridine,

(253) 5-[4-(2-hydroxyethoxy)phenyl]-7-(4-methylpiperazin-1-yl)thieno[2,3-c]pyridine,

(254) 7-(1-ethylpiperazin-4-yl)-5-[4-(1-hydroxypentyl)phenyl]thieno[2,3-c]pyridine,

(255) 7-(1-ethylpiperazin-4-yl)-5-[4-(1-hydroxy-3-methylbutyl)phenyl]thieno[2,3-c]pyridine,

(256) 7-(1-ethylpiperazin-4-yl)-5-[4-(3-hydroxy-1-fluoropropyl)phenyl]thieno[2,3-c]pyridine,

(257) 5-[4-(3-hydroxypropyl)-3-chlorophenyl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine,

(258) 7-(1-ethylpiperazin-4-yl)-5-[3-(2-hydroxyethoxy)phenyl]thieno[2,3-c]pyridine,

(259) 7-(4-ethylpiperazin-1-yl)-5-(4-hydroxyethoxyphenyl)thieno[2,3-c]pyridine,

(260) 7-(1-ethylpiperazin-4-yl)-5-[4-(2-hydroxy-2-methylpropoxy)phenyl]thieno[2,3-c]pyridine,

(261) 5-[3-(3-hydroxypropyl)-4-methoxyphenyl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine,

(262) 5-[4-(3-hydroxypropyl)-3-cyanophenyl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine,

(263) 5-[2-(4-morpholinyl)pyridin-5-yl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine,

(264) 5-[2-(4-thiomorpholinyl)pyridin-5-yl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine,

(265) 5-[2-(4-hydroxypiperidin-1-yl)pyridin-5-yl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine,

(266) 5-[4-(5,6-dihydro-2H-pyran-4-yl)phenyl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine,

(267) 5-[2-(2-methoxyethoxy-2-methyl)pyridin-5-yl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine,

(268) 5-[2-(2-hydroxyethoxy)pyridin-5-yl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine,

(269) 5-[2-(2-methoxyethoxy)pyridin-5-yl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine,

(270) 5-[4-(4-hydroxycyclohexen-1-yl)phenyl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine,

(271) 7-(1-ethylpiperazin-4-yl)-5-(4-pentanoylphenyl)thieno[2,3-c]pyridine,

(272) 7-(1-ethylpiperazin-4-yl)-5-[4-(3-methylbutanoyl)phenyl]thieno[2,3-c]pyridine,

(273) 7-(1-ethylpiperazin-4-yl)-5-[4-(N-cyclohexylamide)phenyl]thieno[2,3-c]pyridinecarboxamide,

(274) 7-(1-ethylpiperazin-4-yl)-5-[4-(pyrrolidinyl-1-carbonyl)phenyl]thieno[2,3-c]pyridine,

(275) 5-[4-(2-hydroxyethoxy)phenyl]-7-[4-(2-hydroxyethyl)piperazin-1-yl]thieno[3,2-c]pyridine,

(276) 5-(4-methoxyphenyl)-7-[4-(2-hydroxyethyl)piperazin-1-yl]thieno[2,3-c]pyridine,

(277) 4-(4-ethylpiperazin-1-yl)-6-(4-methoxyphenyl)thieno[3,4-c]pyridine,

(278) 4-(4-ethylpiperazin-1-yl)-6-[4-(2-hydroxyethoxy)phenyl]thieno[3,4-c]pyridine,

(279) 4-(4-methylpiperazin-1-yl)-6-[4-(2-hydroxyethoxy)phenyl]thieno[3,2-c]pyridine,

(280) 4-(4-ethylpiperazin-1-yl)-6-(4-hydroxyphenyl)thieno[3,2-c]pyridine,

(281) 4-(4-ethylpiperazin-1-yl)-6-[4-(1-hydroxyethyl)phenyl]thieno[3,2-c]pyridine,

(282) 4-(4-ethylpiperazin-1-yl)-6-[4-(1-hydroxypropyl)phenyl]thieno[3,2-c]pyridine,

(283) 4-(4-ethylpiperazin-1-yl)-6-[4-(1-hydroxybutyl)phenyl]thieno[3,2-c]pyridine,

(284) 4-(1-ethylpiperazin-4-yl)-6-[3-(2-hydroxyethoxy)phenyl]thieno[3,2-c]pyridine,

(285) 4-(1-ethylpiperazin-4-yl)-6-[4-(3-hydroxybutyl)phenyl]thieno[3,2-c]pyridine,

(286) (4-ethylpiperazin-1-yl)-6-[4-(2-hydroxyethoxy)phenyl]thieno[3,2-c]pyridine,

(287) 4-(4-ethylpiperazin-1-yl)-6-[4-(2-hydroxypropoxy)phenyl]thieno[3,2-c]pyridine,

(288) 6-[4-(2-methyl-2-hydroxypropoxy)phenyl]-4-(4-methylpiperazin-1-yl)thieno[3,2-c]pyridine,

(289) 6-[4-(2-methyl-2-hydroxypropoxy)phenyl]-4-(4-propylpiperazin-1-yl)thieno[3,2-c]pyridine,

(290) 6-[4-(2-methyl-2-hydroxypropoxy)phenyl]-4-(4-ethylpiperazin-1-yl)thieno[3,2-c]pyridine,

(291) 4-(4-ethylpiperazin-1-yl)-6-[4-(3-hydroxy-3-methylbutyl)phenyl]thieno[3,2-c]pyridine,

(292) 6-[4-(4-methyl-4-hydroxypentyloxy)phenyl]-4-(4-ethylpiperazin-1-yl)thieno[3,2-c]pyridine,

(293) 4-(4-propylpiperazin-1-yl)-6-[4-(2-hydroxyethoxy)phenyl]thieno[3,2-c]pyridine,

(294) 6-[4-(2-methyl-2-hydroxypropoxy)phenyl]-4-[4-(2-fluoroethyl)piperazin-1-yl)thieno[3,2-c]pyridine,

(295) 4-[4-(2-fluoroethyl)piperazin-1-yl]-6-[4-(2-hydroxyethoxy)phenyl]thieno[3,2-c]pyridine,

(296) 6-[4-(2-methyl-2-hydroxypropoxy)phenyl]-4-[4-(2-hydroxyethyl)piperazin-1-yl]thieno[3,2-c]pyridine,

(297) 6-[4-(2-methyl-2-hydroxypropoxy)phenyl]-4-[4-(2-phenylethyl)piperazin-1-yl]thieno[3,2-c]pyridine,

(298) 7-(1-ethylpiperazin-4-yl)-5-[3-(2-hydroxyethoxy)phenyl]furo[2,3-c]pyridine,

(299) 7-(1-ethylpiperazin-4-yl)-5-[4-(3-hydroxypropyl)phenyl]furo[2,3-c]pyridine,

(300) 7-(1-ethylpiperazin-4-yl)-5-[4-(3-hydroxybutyl)phenyl]furo[2,3-c]pyridine,

(301) 7-(1-ethylpiperazin-4-yl)-5-[4-(2-hydroxyethoxy)phenyl]furo[2,3-c]pyridine,

(302) 7-(1-ethylpiperazin-4-yl)-5-{4-[(R)-2-hydroxy-1-methylethoxy]phenyl}furo[2,3-c]pyridine,

(303) 7-(1-ethylpiperazin-4-yl)-5-{4-[(S)-2-hydroxy-1-methylethoxy]phenyl}furo[2,3-c]pyridine,

(304) 7-(1-ethylpiperazin-4-yl)-5-{4-[(S)-2-hydroxypropoxy]phenyl}furo[2,3-c]pyridine,

(305) 7-(1-ethylpiperazin-4-yl)-5-{4-[(R)-2-hydroxypropoxy]phenyl}furo[2,3-c]pyridine,

(306) 7-(1-ethylpiperazin-4-yl)-5-[4-(3-hydroxy-3-methylbutoxy)phenyl]furo[2,3-c]pyridine,

(307) 7-(1-ethylpiperazin-4-yl)-5-{trans-2-[4-(2-hydroxyethoxy)phenyl]ethenyl}furo[2,3-c]pyridine,

(308) 7-(1-ethylpiperazin-4-yl)-5-{trans-2-[2-(2-hydroxyethoxy)phenyl]ethenyl}furo[2,3-c]pyridine,

(309) 1-(1-ethylpiperazin-4-yl)-3-[4-(2-hydroxy-2-methylpropoxy)phenyl]isoquinoline,

(310) 1-(1-ethylpiperazin-4-yl)-3-(3-phenyl-3-hydroxy-1-propynyl)isoquinoline,

(311) 1-(1-ethylpiperazin-4-yl)-8-methyl-3-(4-methoxyphenyl)isoquinoline,

(312) 1-(1-ethylpiperazin-4-yl)-4-methyl-3-(4-methoxyphenyl)isoquinoline,

(313) 1-[1-(2-cyanoethyl)piperazin-4-yl]-3-(4-methoxyphenyl)isoquinoline,

(314) 1-[1-(carbamoylmethyl)piperazin-4-yl]-3-(4-methoxyphenyl)isoquinoline,

(315) 1-(4-ethylsulfonylpiperazin-1-yl)-3-(4-methoxyphenyl)isoquinoline,

(316) 4-piperidinyl-6-[4-(2-methyl-2-hydroxypropoxy)phenyl]thieno[3,2-c]pyridine,

(317) 7-(1-ethylpiperazin-4-yl)-5-[4-(3-hydroxypropoxy)phenyl]furo[2,3-c]pyridine,

(318) 1-(4-ethylpiperazin-1-yl)-3-(4-methoxyphenyl)isoquinoline,

(319) 1-{N-[2-(2-dimethylamino)ethyl]-N-methylamino}-3-(4-methoxyphenyl)isoquinoline,

(320) 1-(4-morpholinyl)-3-(4-methoxyphenyl)isoquinoline,

(321) 1-(1-ethyl-2-pyrrolidinyl)methylamino-3-(4-methoxyphenyl)isoquinoline,

(322) 3-(4-methoxyphenyl)-1-[2-(2-pyridyl)ethyl]aminoisoquinoline,

(323) 1-[2-(4-morpholinyl)ethyl]amino-3-(4-methoxyphenyl)isoquinoline,

(324) 1-(1-imidazolyl)-3-(4-methoxyphenyl)isoquinoline,

(325) 1-[4-(piperidin-1-yl)piperidin-1-yl]-3-(4-methoxyphenyl)isoquinoline,

(326) 1-(1,4,5,6-tetrahydropyrimidin-1-yl)-3-(4-methoxyphenyl)isoquinoline,

(327) 1-(1-ethylhomopiperazin-4-yl)-3-(4-methoxyphenyl)isoquinoline,

(328) 3-(4-methoxyphenyl)-1-(4-ethylpiperazin-1-yl)methylisoquinoline,

(329) 1-(4-ethylpiperazin-1-yl)-3-[3-(2-hydroxyethoxy)phenyl]isoquinoline,

(330) 1-(4-ethylpiperazin-1-yl)-3-(4-ethoxyphenyl)isoquinoline,

(331) 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxypropoxy)phenyl]isoquinoline,

(332) 1-(4-ethylpiperazin-1-yl)-3-(3,4-ethylenedioxyphenyl)isoquinoline,

(333) 1-(4-ethylpiperazin-1-yl)-3-[4-(3-methoxypropyl)phenyl]isoquinoline,

(334) 1-(4-ethylpiperazin-1-yl)-3-[4-(n-butyl)phenyl]isoquinoline,

(335) 1-(4-ethylpiperazin-1-yl)-3-(4-methoxypyridin-2-yl)isoquinoline,

(336) 1-(4-ethylpiperazin-1-yl)-3-[4-(1,3-dioxolan-2-ylmethyloxy)phenyl]isoquinoline,

(337) 1-(4-ethylpiperazin-1-yl)-3-[4-(2,3-dihydroxypropoxy)phenyl]isoquinoline,

(338) 1-(4-ethylpiperazin-1-yl)-3-(4-carbamoylmethoxyphenyl)isoquinoline,

(339) 1-(4-ethylpiperazin-1-yl)-3-(4-trifluoromethoxyphenyl)isoquinoline,

(340) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxyethoxy)-3-methoxyphenyl]isoquinoline,

(341) 1-(4-ethylpiperazin-1-yl)-3-(4-methylthiophenyl)isoquinoline,

(342) 1-(4-ethylpiperazin-1-yl)-3-(4-methylsulfonylphenyl)isoquinoline,

(343) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxy-3-methoxypropoxy)phenyl]isoquinoline,

(344) 1-(4-ethylpiperazin-1-yl)-3-(2-methoxypyridin-5-yl)isoquinoline,

(345) 1-(4-ethylpiperazin-1-yl)-3-[4-(1-hydroxy-1-methylethyl)phenyl]isoquinoline,

(346) 1-(4-ethylpiperazin-1-yl)-3-{4-[N-(2-hydroxyethyl)carbamoyl]phenyl}isoquinoline,

(347) 1-(4-ethylpiperazin-1-yl)-3-{4-[N-(2-hydroxyethyl)sulfamoyl]phenyl}isoquinoline,

(348) 1-(4-ethylpiperazin-1-yl)-3-[4-(1-hydroxyethyl)phenyl]isoquinoline,

(349) 1-(4-ethylpiperazin-1-yl)-3-[4-(propylsulfonyl)phenyl]isoquinoline,

(350) 1-(4-ethylpiperazin-1-yl)-3-{4-[(3-methoxypropyl)sulfonyl]phenyl}isoquinoline,

(351) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxyethyl)phenyl]isoquinoline,

(352) 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxypropyl)sulfonylphenyl]isoquinoline,

(353) 1-(4-ethylpiperazin-1-yl)-3-[4-(N-propylsulfamoyl)phenyl]isoquinoline,

(354) 1-(4-ethylpiperazin-1-yl)-3-{4-[N-(2-methoxyethyl)sulfamoyl]phenyl}isoquinoline,

(355) 1-(4-ethylpiperazin-1-yl)-3-[4-(3-fluoropropyl)sulfonylphenyl]isoquinoline,

(356) 1-(4-ethylpiperazin-1-yl)-3-[4-(pyrrolidin-1-yl)sulfonylphenyl]isoquinoline,

(357) 1-(4-ethylpiperazin-1-yl)-3-[4-(N-ethylsulfamoyl)phenyl]isoquinoline,

(358) 1-(4-ethylpiperazin-1-yl)-3-[4-(N-methyl-N-propylsulfamoyl)phenyl]isoquinoline,

(359) 1-(4-ethylpiperazin-1-yl)-3-[4-(N,N-diethylsulfamoyl)phenyl]isoquinoline,

(360) 1-(4-ethylpiperazin-1-yl)-3-{4-[N-(1-methylpropyl)sulfamoyl]phenyl}isoquinoline,

(361) 1-(4-ethylpiperazin-1-yl)-3-[4-(N-methylsulfamoyl)phenyl]isoquinoline,

(362) 1-(4-ethylpiperazin-1-yl)-3-[4-(N,N-dimethylsulfamoyl)phenyl]isoquinoline,

(363) 1-(4-ethylpiperazin-1-yl)-3-[4-(N-cyclopropylsulfamoyl)phenyl]isoquinoline,

(364) 1-(4-ethylpiperazin-1-yl)-3-[4-(N-ethylcarbamoyl)phenyl]isoquinoline,

(365) 1-(4-ethylpiperazin-1-yl)-3-[4-(N-methylcarbamoyl)phenyl]isoquinoline,

(366) 1-(4-ethylpiperazin-1-yl)-3-[4-(ethylsulfonyl)phenyl]isoquinoline,

(367) 1-(4-ethylpiperazin-1-yl)-3-(3-fluoro-4-methoxyethoxyphenyl)isoquinoline,

(368) 1-(4-ethylpiperazin-1-yl)-3-(3,5-difluoro-4-methoxyethoxyphenyl)isoquinoline,

(369) 1-(4-ethylpiperazin-1-yl)-3-[3-fluoro-4-(2-hydroxyethoxy)phenyl]isoquinoline,

(370) 1-(4-ethylpiperazin-1-yl)-3-[3,5-difluoro-4-(2-hydroxyethoxy)phenyl]isoquinoline,

(371) 1-(4-ethylpiperazin-1-yl)-3-[3,5-difluoro-4-(2-fluoroethoxy)phenyl]isoquinoline,

(372) 1-[4-(2-hydroxyethyl)piperazin-1-yl]-3-[4-(N-ethylsulfamoyl)phenyl]isoquinoline,

(373) 1-[4-(2-hydroxyethyl)piperazin-1-yl]-3-[4-(propylsulfonyl)phenyl]isoquinoline,

(374) 1-(4-ethylpiperazin-1-yl)-3-(phenylthio)isoquinoline,

(375) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-oxopropyl)phenyl]isoquinoline,

(376) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxypropyl)phenyl]isoquinoline,

(377) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxy-2-

methylpropyl)phenyl]isoquinoline,

(378) 1-(4-ethylpiperazin-1-yl)-3-(2-pyridylthio)isoquinoline,

(379) 1-(4-ethylpiperazin-1-yl)-3-(4-butyrylphenyl)isoquinoline,

(380) 1-(4-ethylpiperazin-1-yl)-3-[4-(1-hydroxyiminobutyl)phenyl]isoquinoline,

(381) 1-(4-ethylpiperazin-1-yl)-3-[4-(N-methyl-N-propylcarbamoyl)phenyl]isoquinoline,

(382) 1-(4-ethylpiperazin-1-yl)-3-{4-[N-(2-hydroxyethyl)-N-methylcarbamoyl]phenyl}isoquinoline,

(383) 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxy-1-methylpropyl)phenyl]isoquinoline,

(384) 1-(4-ethylpiperazin-1-yl)-3-[4-(N-propylcarbamoyl)-3-fluorophenyl]isoquinoline,

(385) 1-(4-ethylpiperazin-1-yl)-3-[3-fluoro-4-(2-hydroxyethyl)phenyl]isoquinoline,

(386) 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxy-2-methylpropyl)phenyl]isoquinoline,

(387) 1-(4-ethylpiperazin-1-yl)-3-[4-(1,2-dihydroxyethyl)phenyl]isoquinoline,

(388) 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxy-3-methylbutyl)phenyl]isoquinoline,

(389) 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxy-2,2-dimethylpropyl)phenyl]isoquinoline,

(390) 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxy-1,1-

dimethylpropyl)phenyl]isoquinoline,

(391) 1-(4-ethylpiperazin-1-yl)-3-[4-(1,3-dihydroxy-2,2-dimethylpropyl)phenyl]isoquinoline,

(392) 1-(4-ethylpiperazin-1-yl)-3-{4-[4-(2-hydroxyethyl)tetrahydropyran-4-yl]phenyl}isoquinoline,

(393) 1-(4-ethylpiperazin-1-yl)-3-(2-hydroxymethylindan-5-yl)isoquinoline,

(394) 1-(4-ethylpiperazin-1-yl)-3-[(3,4-dihydroxymethyl)phenyl]isoquinoline,

(395) 1-(4-ethylpiperazin-1-yl)-3-[4-(1,4-dioxan-2-yl)phenyl]isoquinoline,

(396) 1-(4-ethylpiperazin-1-yl)-3-[4-(tetrahydrofuran-2-yl)phenyl]isoquinoline,

(397) 1-(4-ethylpiperazin-1-yl)-3-[4-(cis-4-hydroxycyclohexyl)phenyl]isoquinoline,

(398) 1-(4-ethylpiperazin-1-yl)-3-[4-(trans-4-hydroxycyclohexyl)phenyl]isoquinoline,

(399) 1-(4-ethylpiperazin-1-yl)-3-[4-(tetrahydropyran-4-yl)methylphenyl]isoquinoline,

(400) 4-chloro-1-(4-ethylpiperazin-1-yl)-3-(4-methoxyphenyl)isoquinoline,

(401) 1-(4-ethylpiperazin-1-yl)-3-[4-(cis-4-hydroxytetrahydropyran-2-yl)phenyl]isoquinoline,

(402) 1-(4-ethylpiperazin-1-yl)-3-[4-(trans-4-hydroxytetrahydropyran-2-yl)phenyl]isoquinoline,

(403) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-

hydroxypropoxy)phenyl]isoquinoline,

(404) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxy-1-methylethoxy)phenyl]isoquinoline,

(405) 1-(4-ethylpiperazin-1-yl)-3-(2-methoxypyridin-4-yl)isoquinoline,

(406) 1-(4-ethylpiperazin-1-yl)-3-(2-benzyloxypyridin-4-yl)isoquinoline and 1-(4-ethylpiperazin-1-yl)-3-(2-chloropyridin-4-yl)isoquinoline,

(407) 1-(4-ethylpiperazin-1-yl)-3-[2-(2-methoxyethoxy)pyridin-4-yl]isoquinoline,

(408) 1-(4-ethylpiperazin-1-yl)-3-(4-carbamoylphenyl)isoquinoline,

(409) 1-(4-ethylpiperazin-1-yl)-3-[4-(cyclohexylhydroxymethyl)phenyl]isoquinoline,

(410) 1-(4-ethylpiperazin-1-yl)-3-[4-(4-hydroxytetrahydropyran-4-yl)phenyl]isoquinoline,

(411) 1-(4-ethylpiperazin-1-yl)-3-{4-[bis(1,3-thiazol-2-yl)hydroxymethyl]phenyl}isoquinoline,

(412) 1-(4-ethylpiperazin-1-yl)-3-[4-(1,3-thiazol-2-yl)hydroxymethylphenyl]isoquinoline,

(413) 1-(4-ethylpiperazin-1-yl)-3-[(3-pyridyl)hydroxymethyl]isoquinoline,

(414) 1-(4-ethylpiperazin-1-yl)-3-(1-indanon-5-yl)isoquinoline,

(415) 1-(4-ethylpiperazin-1-yl)-3-(1-hydroxyindan-5-yl)isoquinoline,

(416) 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxy-3-methylbutyl)-3-fluorophenyl]isoquinoline,

(417) 1-(4-ethylpiperazin-1-yl)-3-[3-cyano-4-(2-hydroxyethoxy)phenyl]isoquinoline,

(418) 1-(4-ethylpiperazin-1-yl)-3-[3-(3-hydroxypropyl)phenyl]isoquinoline,

(419) 1-(4-ethylpiperazin-1-yl)-3-benzylisoquinoline,

(420) 1-(4-ethylpiperazin-1-yl)-3-(2-hydroxy-2-phenylethyl)isoquinoline,

(421) 3-benzamide-1-(4-ethylpiperazin-1-yl)isoquinoline,

(422) 3-benzenesulfoneamide-1-(4-ethylpiperazin-1-yl)isoquinoline,

(423) 1-(4-ethylpiperazin-1-yl)-3-(4-methoxybenzenesulfonamide)isoquinoline,

(424) 1-(4-ethylpiperazin-1-yl)-3-(4-methoxyphenoxymethyl)isoquinoline,

(425) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxyethoxy)-2-methoxyphenyl]isoquinoline,

(426) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxycyclohexyloxy)phenyl]isoquinoline,

(427) 4-(4-ethylpiperazin-1-yl)-2-(4-methoxyphenyl)quinazoline,

(428) 1-(4-ethylpiperazin-1-yl)-3-(4-methoxyphenyl)-7-azaisoquinoline,

(429) 7-(4-ethylpiperazin-1-yl)-5-[2-(3-hydroxypropyl)pyridin-5-yl]thieno[2,3-c]pyridine,

(430) 7-(4-ethylpiperazin-1-yl)-5-[3-(2-hydroxyethoxy)styryl]thieno[2,3-c]pyridine,

(431) 7-(4-ethylpiperazin-1-yl)-5-[4-(2-hydroxyethoxy)styryl]thieno[2,3-c]pyridine,

(432) 7-(4-ethylpiperazin-1-yl)-5-[4-(3-hydroxypropyl)phenyl]thieno[2,3-c]pyridine,

(433) 7-(4-ethylpiperazin-1-yl)-5-[4-(3-hydroxypropyl)-3-methoxyphenyl]thieno[2,3-c]pyridine,

(434) 7-(4-ethylpiperazin-1-yl)-5-[4-(3-hydroxypropoxy)phenyl]thieno[2,3-c]pyridine,

(435) 7-(4-ethylpiperazin-1-yl)-5-[4-(2-hydroxypropoxy)phenyl]thieno[2,3-c]pyridine,

(436) 7-(4-ethylpiperazin-1-yl)-5-[4-(2-hydroxypropyl)phenyl]thieno[2,3-c]pyridine,

(437) 7-(4-ethylpiperazin-1-yl)-5-[3-chloro-4-(2-hydroxyethoxy)phenyl]thieno[2,3-c]pyridine,

(438) 7-(4-ethylpiperazin-1-yl)-5-[4-(1-methyl-2-hydroxyethoxy)phenyl]thieno[2,3-c]pyridine,

(439) 7-(4-ethylpiperazin-1-yl)-5-[4-(3-hydroxy-3-methylbutyl)phenyl]thieno[2,3-c]pyridine,

(440) 7-(4-ethylpiperazin-1-yl)-5-[4-(3-hydroxybutyl)phenyl]thieno[2,3-c]pyridine,

(441) 7-(4-ethylpiperazin-1-yl)-5-[4-(3-hydroxy-2-methylpropyl)phenyl]thieno[2,3-c]pyridine,

(442) 7-(4-ethylpiperazin-1-yl)-5-[4-(3-hydroxy-2,2-dimethylpropyl)phenyl]thieno[2,3-c]pyridine,

(443) 7-(4-ethylpiperazin-1-yl)-5-[4-(3-hydroxy-1,1-dimethylpropyl)phenyl]thieno[2,3-c]pyridine,

(444) 7-(4-ethylpiperazin-1-yl)-5-[4-(2-hydroxypropylthio)phenyl]thieno[2,3-c]pyridine,

(445) 7-(4-ethylpiperazin-1-yl)-5-(4-methanesulfonylphenyl)thieno[2,3-c]pyridine,

(446) 7-(4-ethylpiperazin-1-yl)-5-[4-(1-hydroxybutyl)phenyl]thieno[2,3-c]pyridine,

(447) 7-(4-ethylpiperazin-1-yl)-5-[4-(N-methylcarbamoyl)phenyl]thieno[2,3-c]pyridine,

(448) 7-(4-ethylpiperazin-1-yl)-5-[4-(N-ethylcarbamoyl)phenyl]thieno[2,3-c]pyridine,

(449) 7-(4-ethylpiperazin-1-yl)-5-[4-(N-propylcarbamoyl)phenyl]thieno[2,3-c]pyridine,

(450) 7-(4-ethylpiperazin-1-yl)-5-(4-ethanesulfonylphenyl]thieno[2,3-c]pyridine,

(451) 7-(4-ethylpiperazin-1-yl)-5-(4-propanesulfonylphenyl)thieno[2,3-c]pyridine,

(452) 7-(4-ethylpiperazin-1-yl)-5-[4-(N-butylcarbamoyl)phenyl]thieno[2,3-c]pyridine,

(453) 7-(4-ethylpiperazin-1-yl)-5-[4-(N-cyclopentylcarbamoyl)phenyl]thieno[2,3-c]pyridine,

(454) 7-(4-ethylpiperazin-1-yl)-5-[4-(cis-4-hydroxytetrahydropyran-2-yl)phenyl]thieno[2,3-c]pyridine,

(455) 7-(4-ethylpiperazin-1-yl)-5-[4-(trans-4-hydroxytetrahydropyran-2-yl)phenyl]thieno[2,3-c]pyridine,

(456) 7-(4-ethylpiperazin-1-yl)-5-(2,3-dihydro-2-hydroxymethyl-2-methylbenzofuran-5-yl)phenyl]thieno[2,3-c]pyridine,

(457) 7-(4-ethylpiperazin-1-yl)-5-[4-(cyclohexylhydroxymethyl)phenyl]thieno[2,3-c]pyridine,

(458) 7-(4-ethylpiperazin-1-yl)-5-[4-(cyclopentylhydroxymethyl)phenyl]thieno[2,3-c]pyridine,

(459) 7-(4-ethylpiperazin-1-yl)-5-(4-methoxyphenyl)thieno[2,3-c]pyridine,

(460) 4-(4-ethylpiperazin-1-yl)-6-[4-(1,3-dioxolan-2-yl)methoxyphenyl]thieno[3,2-c]pyridine,

(461) 4-(4-ethylpiperazin-1-yl)-6-[4-(2-hydroxyethoxy)phenyl]thieno[3,2-c]pyridine,

(462) 4-(4-ethylpiperazin-1-yl)-6-[4-(3-hydroxypropoxy)phenyl]thieno[3,2-c]pyridine,

(463) 4-(4-ethylpiperazin-1-yl)-6-[4-(2-hydroxy-1-methylethoxy)phenyl]thieno[3,2-c]pyridine,

(464) 4-(4-ethylpiperazin-1-yl)-6-[4-(3-hydroxy-1-propynyl)phenyl]thieno[3,2-c]pyridine,

(465) 4-(4-ethylpiperazin-1-yl)-6-[4-(3-hydroxypropyl)phenyl]thieno[3,2-c]pyridine,

(466) 4-(4-ethylpiperazin-1-yl)-6-[4-(3-hydroxy-3-methyl-1-butynyl)phenyl]thieno[3,2-c]pyridine,

(467) 7-(4-ethylpiperazin-1-yl)-5-(4-methoxyphenyl)furo[2,3-c]pyridine and

(468) 4-(4-ethylpiperazin-1-yl)-6-(4-

methoxyphenyl)furo[3,2-c]pyridine.

Among the condensed pyridine compound according to the present invention, those which are particularly preferable from the viewpoint of pharmacological effects or safety are, for example, the following ones:

(1) 1-(4-ethylpiperazin-1-yl)-3-[4-(1-hydroxypropyl)phenyl]isoquinoline,

(2) 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxypropyl)phenyl]isoquinoline,

(3) 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxybutyl)phenyl]isoquinoline,

(4) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxyethoxy)phenyl]isoquinoline,

(5) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-methoxyethoxy)phenyl]isoquinoline,

(6) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-fluoroethoxy)phenyl]isoquinoline,

(7) 3-[4-(2-cyanoethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(8) 7-(4-ethylpiperazin-1-yl)-5-(4-hydroxyethoxyphenyl)thieno[2,3-c]pyridine,

(9) (4-ethylpiperazin-1-yl)-6-[4-(2-hydroxyethoxy)phenyl]thieno[3,2-c]pyridine,

(10) 4-(4-ethylpiperazin-1-yl)-6-[4-(2-hydroxypropoxy)phenyl]thieno[3,2-c]pyridine and

(11) 6-[4-(2-methyl-2-hydroxy)propoxyphenyl]-(4-

ethylpiperazin-1-yl)thieno[3,2-c]pyridine.

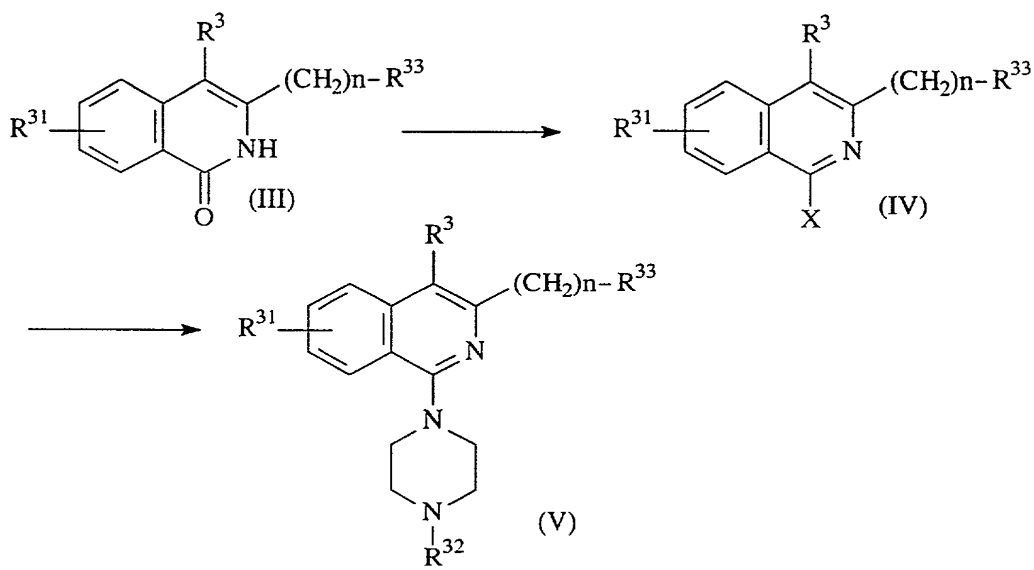
Although some of the condensed pyridine compound of the present invention occur as stereomers, either one of these stereomers or a mixture thereof may be used in the present invention without restriction. Similarly, either one of geometrical isomers or a mixture thereof may be employed herein without any restriction. In the case of polymorphic crystals, either one of the crystal forms or a mixture thereof may be used in the present invention without restriction, too. Moreover, use may be made of both anhydrides and hydrates.

The pharmacologically acceptable salts to be used in the present invention may be arbitrary salts of the condensed pyridine compound of the present invention without particular restriction. Examples thereof include inorganic acid addition salts such as hydrochlorides, sulfates, nitrates, hydrobromides, hydriodides, perchlorates and phosphates, organic acid addition salts such as oxalates, maleates, fumarates and succinates, sulfonic acid addition salts such as methanesulfonates, ethanesulfonates, benzenesulfonates, p-toluenesulfonates and camphorsulfonates, and amino acid addition salts. Among all, it is preferable to use hydrochlorides and oxalates thereof.

Sequentially, a general process of producing the compound of the present invention will be described below, with no limitation. It can be prepared by other synthetic routes.

(1) The formula of the condensed pyridine compound (I) according to the present invention, in which ring A is benzene ring

The compound can be prepared by reacting isoquinolin-1-one compound (III) with a halogenating agent to give 1-halogenated isoquinoline compound (IV), and reacting the resulting compound which piperazine or 1-substituted piperazine. (See the following formulae. In the formulae, R^3, R^{31}, R^{32}, R^{33} and n have the same meanings as described above. X represents halogen atom.)



Herein, the isoquinolin-1-one compound (III) includes a great number of known compounds, which are available as industrial raw materials or reagents. And, These compound can be produced by methods described in known references.

The isoquinolin-1-one compound (III) can be halogenated by general methods. Herein, any type of halogenating agents can be used, with no limitation. Generally, phosphorus

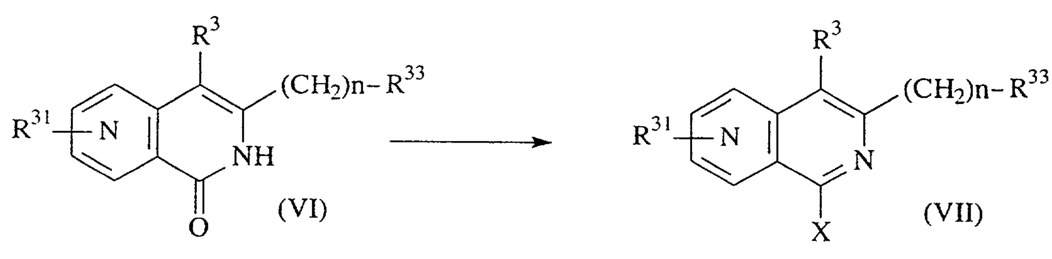
oxychloride, phosphorus trichloride, phosphorus pentachloride, thionyl chloride, sulfuryl chloride, oxazolyl chloride, phosphorus oxybromide, phosphorus tribromide and the like are used; among them, phosphorus oxychloride is preferable.

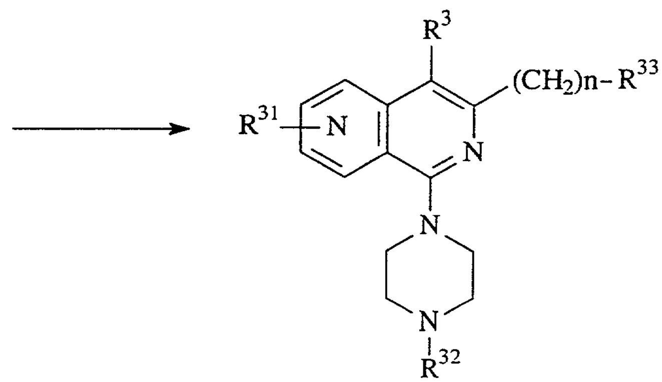
The reaction of the 1-halogenated isoquinoline compound (IV) with piperazine or 1-substituted piperazine can be effected by general methods for N-alkylation.

By chemically modifying the substituent of the 1-piperidylisoquinoline compound (V) thus prepared, furthermore, a novel 1-piperidylisoquinoline compound (V) can be derived.

(2) The formula of the condensed pyridine compound (I) according to the present invention, in which ring A is pyridine ring

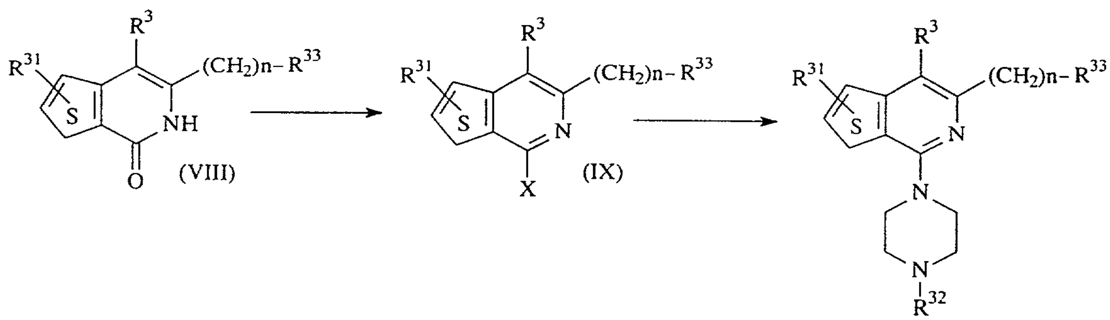
Also in this case, in the same manner as described above in (1), the compound can be prepared by reacting dihydropyridopyridin-8-one compound (VI) with a halogenating agent to give 8-halogenated pyridopyridine compound (VII), and then reacting the resulting compound with piperazine or 1-substituted piperazine. (See the following formulae. In the formulae, R^3, R^{31}, R^{32}, R^{33} and n have the same meanings as described above. X represents halogen atom.)





<u>(3) The formula of the condensed pyridine compound (I) according to the present invention, in which ring A is thiophene ring</u>

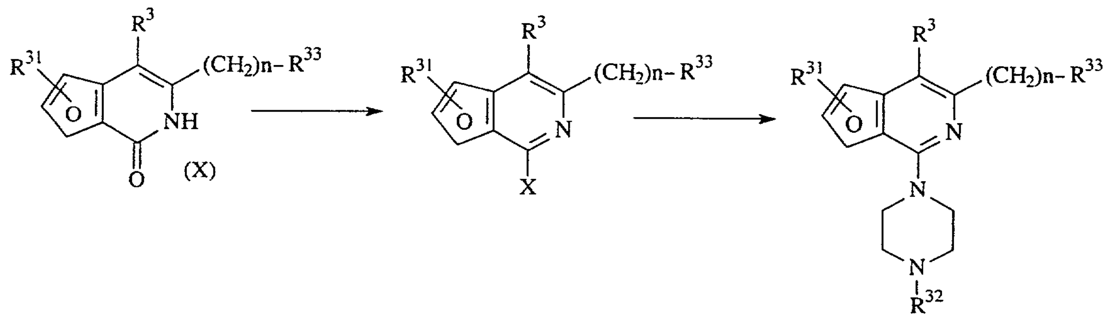
Also in this case, in the same manner as described above in (1) or (2), the compound can be prepared by reacting thienopyridopyridin-7-one compound (VIII) with a halogenating agent to give 7-halogenated thienopyridine compound (IX), and then reacting the resulting compound with piperazine or 1-substituted piperazine. (See the following formulae. In the formulae, R^3, R^{31}, R^{32}, R^{33} and n have the same meanings as described above. X represents halogen atom.)



<u>(4) The formula of the condensed pyridine compound (I) according to the present invention, in which ring A is furan ring</u>

Also in this case, in the same manner as described above in any of (1) to (3), the compound can be prepared by reacting

furopyridin-7-one compound (X) with a halogenating agent to give 7-halogenated furopyridine compound (XI), and then reacting the resulting compound with piperazine or 1-substituted piperazine. (See the following formulae. In the formulae, R^3, R^{31}, R^{32}, R^{33} and n have the same meanings as described above. X represents halogen atom.)



Examples of the dosage forms of the compounds of the present invention include oral preparations such as powders, fine granules, granules, tablets, coated tablets and capsules, external preparations such as ointments, patches and suppositories, and injections. These preparations may be produced by the conventional methods with the use of pharmaceutical carriers commonly employed in the art.

Namely, oral preparations may be produced by blending the 1,4-substituted cyclic amine derivative or a pharmacologically acceptable salt thereof with fillers optionally together with binders, disintegrating agents, lubricating agents, coloring agents, corrigents, etc. and then processing the resultant blends into powders, fine granules, granules, tablets, coated tablets, capsules, etc. by the conventional methods.

As the fillers, use may be made of, for example, lactose,

corn starch, sucrose, glucose, mannitol, sorbitol, crystalline cellulose and silicon dioxide. As the binders, use may be made of, for example, polyvinyl alcohol, polyvinyl ether, methylcellulose, ethylcellulose, acacia, tragacanth, gelatin, shellac, hydroxypropylmethylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, polypropylene glycol/polyoxyethylene block polymers and meglumine. As the disintegrating agents, use may be made of, for example, starch, agar, gelatin powder, crystalline cellulose, calcium carbonate, sodium hydrogencarbonate, calcium citrate, dextrin, pectin and calcium carboxymethylcellulose. As the lubricating agents, use may be made of, for example, magnesium stearate, talc, polyethylene glycol, silica and hardened vegetable oils. As the coloring agents, use may be made of those authorized as pharmaceutical additives. As the corrigents, use may be made of, for example, cocoa powder, mentha, aromatic powder, mentha oil, borneol and powdered cinnamon bark. Needless to say, these tablets and granules may be appropriately coated with sugar, etc., if necessary.

Injections are produced by blending the condensed pyridine compound or a pharmacologically acceptable salt thereof with pH regulating agents, resolvents, tonicity agents, etc., optionally together with dissolution aids, stabilizers, etc. and processing the resultant blends into preparations by the conventional methods.

External preparations may be produced by the conventional

methods without restriction. As the bases, therefore, use can be made of various materials commonly used in drugs, quasi drugs, cosmetics, etc.

Particular examples of the base materials include animal and vegetable oils, mineral oils, ester oils, waxes, higher alcohols, fatty acids, silicone oils, surfactants, phospholipids, alcohols, polyhydric alcohols, water-soluble polymers, clay minerals and purified water. If needed, it is possible to further add pH regulating agents, antioxidants, chelating agents, antiseptics, fungicides, coloring agents, perfumes, etc., though the materials usable as the base in the external preparations of the present invention are not restricted thereto. If necessary, it is also possible to furthermore add other ingredients capable of inducing differentiation, blood flow accelerators, bactericides, antiinflammatory agents, cell activators, vitamins, amino acids, humectants, keratolytic agents, etc. The above materials may be added in such amounts as to give the concentrations thereof commonly employed in the production of external preparations.

The clinical dose of the condensed pyridine compound of the present invention or a pharmacologically acceptable salt thereof is not restricted but varies depending on the symptoms, severity, age, complications, etc. Also, the dose thereof varies depending on the type of the salt, administration route, etc. In general, these compounds are administered to an adult

in a dose of from 0.01 to 1000 mg, preferably from 0.1 to 500 mg and still preferably from 0.5 to 100 mg, per day orally, intravenously, as suppositories or percutaneously.

Next, the results of a binding test on the compounds of the present invention to serotonin 1A and serotonin 2 receptors will be given so as to illustrate the effects of the present invention. Moreover, the results of a binding test on these compounds to an α_1 adrenalin receptor will be given so as to illustrate the safety thereof.

It is reported in, for example, the following publications that compounds with a serotonin antagonism are usable as medicament for treating, ameliorating and preventing spastic paralysis or central muscle relaxants for ameliorating myotonia:

(1) Saishin Igaku Jiten, 3rd impression of 1st edition, p. 809 "SEROTONIN", Iyaku Shuppan

(2) Stedman's Medical Dictionary, 24th edition, p. 1227 "serotonin", Williams & Wilkins

(3) Shinkei Shinpo, 37(3), 459 - 467, 1993.

(4) Iyaku Journal, 30(8), 2030 - 2068, 1994.

(5) DN & P, 5(8), 453 - 460, 1992.

(6) Annals of Neurology, 30(4), 533 - 541, 1991.

Compounds poor in the ability to bind to an α_1 adrenalin receptor are medicines which would scarcely affect blood pressure in orthostatic hypotension, etc. and have a higher safety.

(1) Binding test on serotonin 1A, serotonin 2 and α_1 adrenalin receptors

Method

(Reagent)

The following reagents were employed in this test.

1) Serotonin binoxalate (5-HT binoxalate, mfd. by Sigma Chemical Co.).

2) Methysergide maleate (mfd. by RBI).

As radioisotope-labeled compounds, use was made of the following reagents (mfd. by NEN).

3) [^{3}H] 8-Hydroxy-dipropylaminotetralin (8-OH-DPAT).

4) [^{3}H] Ketanserin hydrochloride.

5) [^{3}H] Prazosin.

These compounds and test compounds, when insoluble in water, were dissolved in ethanol and then diluted with distilled water so as to each give an ethanol concentration of 10%. Methysergide maleate was dissolved in distilled water before using.

(Animal)

Use was made of SD rats aged 6 to 8 weeks.

(Preparation of receptor source)

The rats were sacrificed by dcapitation to extirpate the cerebra. The hippocampus and cortex were separated therefrom and employed in the binding tests respectively on the serotonin 1A receptor and the serotonin 2 receptor.

The hippocampus was mixed with 50 times (on the wet weight

basis) as much a 0.32 M sucrose solution while the cortex was mixed with 10 times as much the same solution. Each mixture was homogenized by using a Teflon glass homogenizer and centrifuged at 1,000 $\times$ g for 10 min. The supernatant thus obtained was further centrifuged at 20,000 $\times$ g for 20 min. The obtained precipitate was re-suspended in 50 times (based on the intial wet weight; in the case of the hippocampus) or 10 times (in the case of the cortex) as much a 50 mM Tris hydrochloride (pH 7.4) and incubated at room temperature for 30 min. After centrifuging at 20,000 $\times$ g for 20 min, the obtained precipitate was further suspended and centrifuged twice each in the same manner. The precipitate thus obtained was suspended in 100 times (based on the initial wet weight; in the case of the hippocampus) or 20 times (in the case of the cortex) as much a 50 mM Tris hydrochloride solution (pH 7.4) to thereby give a receptor fraction. This receptor fraction was stored at -80°C until using.

(Binding test on [^{3}H] 8-hydroxy-dipropylaminotetralin)

To the receptor fraction of the hippocampus were added a test compound and 0.5 nM of [^{3}H] 8-hydroxy-dipropylamino-tetralin and the resultant mixture was incubated at room temperature for 30 min. Next, it was filtered through a glass filter with the use of a cell harvester. After washing the glass filter with 50 mM Tris hydrochloride (pH 7.4), the radioactivity of the receptor was measured with a liquid scintillation counter. The binding detected in the presence of 10 μM of serotonin

binoxalate was referred to as the nonspecific binding.

(Binding test on [^{3}H] ketanserin)

To the receptor fraction of the cerebral cortex were added a test compound and 0.3 nM of [^{3}H] ketanserin and the resultant mixture was incubated at 37℃ for 15 min. Next, it was filtered through a glass filter with the use of a cell harvester. After washing the glass filter with 50 mM Tris hydrochloride (pH 7.4), the radioactivity of the receptor was measured with a liquid scintillation counter. The binding detected in the presence of 1 μM of methysergide was referred to as the nonspecific binding.

IC_{50} was calculated by the probit method, while Ki was determined in accordance with the following formula:

$$Ki = IC_{50}/(1 + c/Kd)$$

wherein c represents the concentration of the radioisotope-labeled compound, and Kd represents the dissociation constant of the radioisotope-labeled compound with respect to the receptor determined by Scatchard's analysis.

(Binding test on [^{3}H] prazosin)

To the receptor fraction of the cerebral cortex were added a test compound and about 0.2 nM of [^{3}H] prazosin and the resultant mixture was incubated at room temperature for 60 min. Next, it was filtered through a glass filter with the use of a cell harvester. After washing the glass filter with 50 mM Tris hydrochloride (pH 7.4), the radioactivity of the receptor was measured with a liquid scintillation counter. The binding

detected in the presence of 10 μM of phentolamine was referred to as the nonspecific binding.

The following tables show the abilities of typical examples of the compounds of the present invention to bind to the serotonin (5HT)1A and serotonin (5HT)2 receptors, wherein the number of each compound corresponds to the number of Example described below. Also, comparison was made with cyproheptadine hydrochloride and cyclobenzaprine hydrochloride which were employed as positive controls having anti-serotonin effects.

Example No.	5HT1(nM)	5HT2(nM)
1	21.2	36.4
3	65	3.8
4	71	74.9
5	21	2.2
7	27.9	81.3
9	57	24.5
10	60	11
12	140	5.32
14	23	35
15	55.5	19.5
16	30	44
17	11.1	26.8

19	6.9	1.6
20	14.5	2.6
21	17.2	4.3
22	9.4	1.5
23	16.8	6.4
24	11.7	7.4
25	21.5	3.4
26	8.5	55
27	29.42	2.47
28	24.4	9.1
29	9.6	3.5
30	10.7	6.3
31	10.7	30.3
32	10.1	7.8
33	7.9	10.9
34	23.5	17.3
35	35.3	5.7
36	18.8	3.9
38	20.8	75.7
39	26	4.9
40	26.7	3.1
41	40.1	45.6
42	33.1	4.4
43	29.3	66.6
44	55.4	9
45	45	1.1

46	58	12.7
47	25.3	2.6
50	25.2	21.9
51	102.77	1.87
52	23.5	0.6
53	61.25	1.78
54	62.1	4.9
55	10.4	15.3
56	37.4	59.5
57	57.2	4.6
58	23.3	18.7
59	16.3	14.3
60	21.3	9.1
61	11.7	8.2
62	14.8	4
63	18.1	0.84
64	86.99	8.5
65	60.1	33.5
66	52.7	21.6
67	27.3	6.6
68	30.9	94.1
69	17.2	17.3
70	23.3	5.5
71	2	1.5
72	15	3.6
73	13	3.3

74	4.6	7.7
75	7.7	10
76	5.7	8.9
77	13.6	90.5
78	0.56	1.9
79	5.8	23
80	0.8	16.3
81	1.1	15.1
82	0.2	10.8
83	75.6	4.3
84	72.1	0.9
85	18.7	9.7
86	11.7	5.3
87	16.9	17
88	9.4	11.7
89	6.3	10
90	4.5	12.9
91	1.1	1.6
92	0.9	0.7
93	10.8	56.7
94	6.4	41.2
95	7.8	21.2
96	138.4	0.1
97	34.7	13.3
98	61.6	2.7
99	3.5	6.2

100	12.7	5.6
102	129.36	132.01
104	108.71	100.93
106	70	30.6
108	156.65	33.76
110	58.62	108.98
111	10.28	89.9
114	167.03	49.89
122	40.1	19.9
123	34	29.1
125	27.1	6.9
126	26.4	5.7
128	22.2	3
129	21.6	18.4
130	24.4	17
131	6.4	5.8
132	1.5	23.4
133	2.9	6.2
134	4.9	12.4
135	3.4	18.9
136	3.7	11.6
137	7.2	32.5
138	13.5	5.5
139	2.7	5.1
140	22.1	36.7
141	2.9	20.4

142	3.3	15.2
143	2.2	17.4
144	4.8	12.4
145	7.5	3.7
146	170.5	2.9
147	6.5	1.7
148	6.33	7.85
149	37.2	21.8
150	10.7	0.8
151	7	79.2
152	6.1	12.4
153	12.9	1.5
154	1.6	8.8
155	19.98	4.34
156	10.93	0.01
157	29.7	4.9
158	0.41	1.08
159	0.65	13.25
160	22.2	0.7
161	10.7	23.8
162	10.7	84.7
163	25.1	19.2
164	9.38	11.88
165	32.58	25.38
166	81.89	11.49
170	3	25.4

171	4.7	21.9
172	4.7	36.2
173	3.9	4.8
174	29.1	7.3
176	154.55	12.38
177	45	0.5
178	56.4	0.2
179	5.3	0.4
181	17.9	6.7
182	10	15.89
183	14.1	3.36
184	30.85	122.2
185	21.21	2
186	2.83	4.5
187	9.81	2.53
188	4.47	106.9
189	37.17	0.44
190	35	3.85
191	12.98	0.93
192	66.74	7.85
194	11.21	33.72
195	22.96	37.22
196	66.74	6.44
197	70.69	4.26
198	45.5	9.08
199	3.27	3.8

200	77.3	7.33
201	35.9	2.96
202	14.61	2.22
203	5.5	0.52
204	25.46	18.54
205	33.15	0.98
206	77.12	2.59
207	22.23	17.95
208	91.61	7.62
209	3.28	2.35
210	6.56	3.95
211	5.17	40.2
213	21.1	31.82
214	15.59	7.59
215	51.93	20.86
216	16.55	15.53
219	2.99	5.92
220	0.53	2.01
233	200	1.97
234	128.78	1.11
243	13	6.7
244	27.14	78.55
245	109.44	72.17
246	86.99	13.91
247	25.08	28.72
248	42.98	31.57

249	37.96	28.08
250	122.76	7.67
253	75.37	5.98
254	59.73	29.18
255	75.37	40.04
256	9.22	19.48
257	12.58	23.23
258	24.72	35.1
259	9.26	18.86
260	67.79	0.54
261	53.74	0.06
262	9.04	0.25
263	6.42	0.89
264	61.35	3.34
265	9.73	113.91
266	97.26	13.78
267	10.39	68.74
268	16.51	85.99
269	15.53	58.38
270	42.98	30.32
272	159.51	22.45
273	51.44	9.11
276	159.51	0.45
277	71.36	52.06
278	41.28	4.61
279	76.43	1.44

281	15.03	16.92
282	10.79	6.46
283	5.71	6.43
284	91.86	75.86
285	22.18	1.96
286	6.95	3.95
287	27.91	0.87
288	80.94	0.14
290	54.87	1.35
291	43.3	1.44
292	68.62	22.45
298	1.72	5.37
299	0.37	30.14
300	0.49	9.06
301	9.15	12.73
302	0.53	30
303	0.53	44.42
304	15.44	19.42
305	18.47	33.12
306	47.73	0.82
307	7.7	11.47
308	6.49	19.46
309	91	0.01
310	4.4	10.18
317	12.24	105.36
329	31.6	73.6

331	23.6	5.9
332	13.9	12.1
333	17.1	6.1
335	60.1	20.3
336	45.7	2.6
337	25.7	5.6
338	14.1	61.9
339	214	18.9
340	26.0	20.7
342	6.2	14.9
343	35.7	5.7
344	10.7	35.9
345	11.3	1.4
346	31.8	41.7
347	8.0	24.2
348	11.0	1.6
349	3.2	5.0
350	2.6	16.7
351	15.7	6.4
352	4.0	54.6
353	1.1	0.24
354	3.0	1.3
355	2.6	4.9
356	2.1	24.2
357	2.8	0.58
358	6.4	19.1

359	6.1	3.2
360	2.0	1.5
361	3.5	2.6
362	4.5	24.1
363	3.5	0.61
364	21.7	3.9
365	26.2	9.9
366	3.8	7.2
367	55.2	3.3
368	32.0	9.1
369	28.2	2.5
370	23.9	3.4
371	41.0	4.3
374	44.5	24.7
375	30.5	7.6
376	19.5	6.3
377	28.5	16.5
378	42.7	95.2
380	31.2	23.0
381	11.1	27.3
383	7.4	3.4
384	27.3	0.1
385	14.8	21.6
386	8.9	2.4
387	25.1	24.7
388	21.5	0.7

389		14.2	7.3
390		7.5	11.1
391		3.6	12.8
393		13.1	1.8
394		10.7	32.9
395		37.3	4.8
396		50.4	2.6
397		53.3	0.9
398		8.0	5.9
399		53.0	17.2
401		31.3	3.4
402		23.7	2.1
403		28.35	0.78
404		18.76	1.07
405		22.6	10.2
406	2-Benzyloxy	46.0	88.1
	2-chloro	12.2	11.1
407		17.8	26.1
408		19.8	36.3
409		16.4	9.7
410		21.1	2.1
412		19.1	41.4
414		17.3	4.2
415		3.6	11.6
416		31.2	0.7
417		13.4	4.5

418	54.5	17.4
419	94.8	16.4
420	117.4	22.4
421	9.47	129.2
422	5.32	175.3
423	9.81	332.47
424	61.6	1.93
425	320.58	2.55
426	132.70	7.10
427	80.94	300.37
430	2.48	11.68
431	1.98	2.11
432	1.98	28.48
433	20.63	3.53
434	64.88	60.48
435	61.18	1.14
436	8.64	26.03
437	30.49	18.11
438	62.94	18.83
439	44.18	6.03
440	21.83	0.72
441	15.23	0.41
442	23.23	2.66
443	10.24	1.85
444	43.16	11.98
445	5.46	90.37

446	12.20	29.96
448	22.60	345.80
449	24.04	43.79
450	6.89	15.16
451	7.72	37.86
452	19.61	7.04
453	22.18	45.39
454	67.41	26.53
455	50.33	39.99
456	63.33	16.21
457	63.33	280.93
458	75.37	93.12
459	107.86	60.15
460	5.32	175.3
461	0.17	15.21
462	4.83	2.84
463	6.98	20.86
464	47.81	1.40
465	6.28	7.11
466	49.8	1.0
467	20.55	93.11
Cyproheptadine	29.5	1.68
Cyclobenzaprine	25	29

Subsequently, the abilities of typical examples of the compounds of the present invention to bind to the $\alpha 1$ adrenalin receptor were evaluated by the test method described above. The following table shows the results, wherein the number of each compound corresponds to the number of Example described below.

Example No.	$\alpha 1$ (nM)
1	>2000
7	521
12	4111
19	373
20	868
21	636
22	3095
23	1253
29	668
32	500
33	758
36	1220
42	2450
45	1220
52	555
63	252
70	1260
73	699

109	>2000
123	553
126	382
139	374
160	536
173	284
179	208
181	920
183	577
185	741
187	969
200	755
202	>2000
220	3803
242	1788
259	405
281	345
286	305
289	1306
300	>2000
331	721.5
393	241.8
416	173.5
Cyproheptadine	1900

The above results indicate that the condensed pyridine compound of the present invention are useful as medicaments with a serotonin antagonism and have clinical usefulness and a high safety, in particular, those for treating, ameliorating and preventing spastic paralysis or central muscle relaxants for ameliorating myotonia.

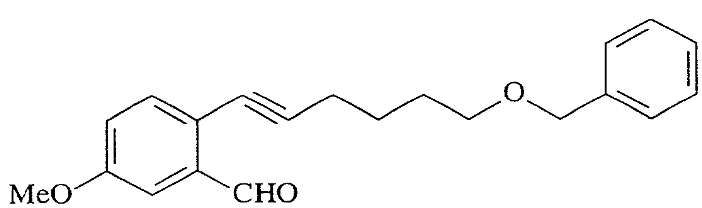
Moreover, it is also evident that the compounds of the present invention are superior in safety, since they have low abilities to bond to the α_1 adrenalin receptor and scarcely affect blood pressure.

Next, to illustrate the present invention in detail, Examples will be given below. However, it is needless to say that the present invention is not restricted thereto.

Examples

Example 1 Synthesis of 3-(4-benzyloxybutyl)-1-(4-ethylpiperazin-1-yl)isoquinoline dihydrochloride

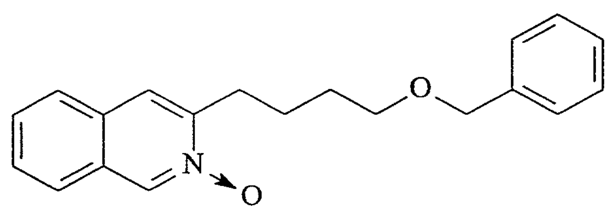
(1-1) 2-[2-(4-Benzyloxybutyl)ethynyl]-5-methoxybenzaldehyde



6-Benzyloxy-1-hexyne (5.60 g) and 2-bromo-benzaldehyde (2.90 g) were reacted in dimethylformamide (30 ml), in the presence of dichloro-bis-triphenylphosphinepalladium (0.40 g), cuprous iodide (0.20 g) and triethylamine (2.5 ml) in nitrogen

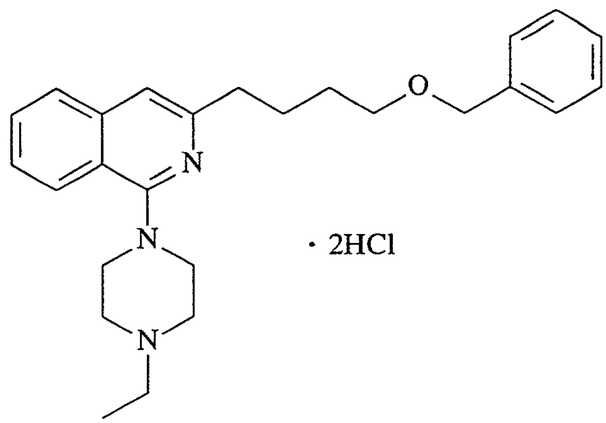
atmosphere at 50°C for 6 hr. The resulting reaction solution was evaporated, and ethyl acetate and water were added to the resulting residue. The resulting organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give 2.60 g of the title compound as a pale yellow oil.

(1-2) 3-(4-Benzyloxybutyl)isoquinoline-2-oxide



2-[2-(4-Benzyloxybutyl)ethynyl]-5-methoxybenzaldehyde (2.60 g), hydroxylamine hydrochloride (0.63 g) and sodium acetate (0.78 g) were reacted in ethanol (30 ml) at 60°C for 2 hr. Potassium carbonate (2.0 g) and water (5 ml) were added to the resulting reaction mixture, which was then heated under reflux for 12 hr. The reaction solution was evaporated, and the resulting residue was extracted with methylene chloride, washed with brine, and then dried. The solvent was removed and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 2.0 g of the title compound as a brown amorphous.

(1-3) 3-(4-Benzyloxybutyl)-1-(4-ethylpiperazin-1-yl)isoquinoline



3-(4-Benzyloxybutyl)isoquinoline-2-oxide (2.0 g) and phosphorous oxychloride (5 ml) were reacted at 110 °C for 2 hr. The reaction solution was evaporated, to the resulting residue were added ethyl acetate and aqueous solution of saturated sodium bicarbonate, and the resulting organic layer was washed with water and brine. The organic layer was dried over magnesium sulfate followed by evaporating the solvent. The resulting 1-chloro-3-(4-benzyloxybutyl)isoquinoline obtained as a yellow oil was reacted with N-ethylpiperazine (5 ml) and potassium carbonate (0.5 g) at 120 °C for 5 hr. The reaction solution was then cooled and then partitioned by adding ethyl acetate and water thereto. The resulting organic layer was washe with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system) to give 1.32 g of the free compound of the title compound as a pale yellow oil.

Free compound:

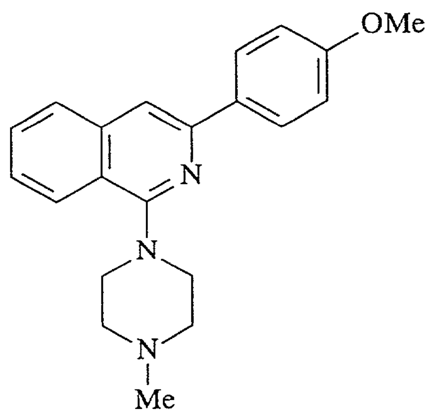
^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 1.64-

1.75(m,2H), 1.80-1.92(m,2H), 2.54(q,J=7.2Hz,2H), 2.74(m,4H), 2.80(t,J=7.2Hz,2H), 3.41-3.56(m,4H), 4.49(s,2H), 7.02(s,1H), 7.22-7.36(m,5H), 7.40(t,J=8.0Hz,1H), 7.53(t,J=8.0Hz,1H), 7.64(d,J=8.0Hz,2H), 8.01(d,J=8.0Hz,2H).

MS(FAB) m/z 404$(M+H)^+$.

The resulting free compound was convereted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/ether, to give 1.14 g of the title compound as a yellow amorphous.

Example 2 Synthesis of 1-(1-methylpiperazin-4-yl)-3-(4-methoxyphenyl)isoquinoline



1-Chloro-3-(4-methoxyphenyl)isoquinoline (526 mg) and 1-methylpiperazine (4.4 ml) were stirred at 120 °C overnight. The reaction mixture was evaporated, aqueous solution of saturated sodium bicarbonate was added thereto, followed by extracting with ethyl acetate. The resulting organic layer was washed with water, dried (over $MgSO_4$), evaporated, and then purified by silica gel column chromatography (methylene chloride/methanol system). The resulting product was

converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol, to give the hydrochloride of the title compound as pale yellow crystals (320 mg, yield; 40%).

Hydrochloride:

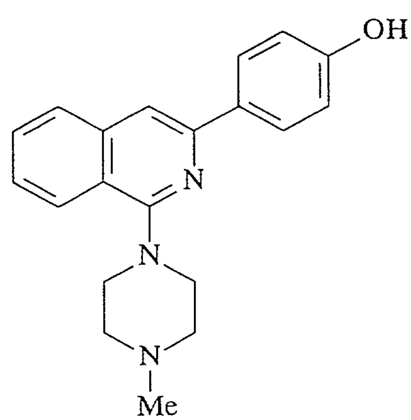
m.p.; 134-136℃

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 2.86(3H,d,J=4.4Hz), 3.26-3.44(4H,m), 3.54(2H,d,J=11.6Hz), 3.80(3H,s), 3.97(2H,d,J=11.6Hz), 7.05(2H,d,J=8.8Hz), 7.55(1H,ddd,J=8.2Hz,6.8Hz,1.2Hz), 7.70(1H,ddd,J=8.2Hz,6.8Hz,1.2Hz), 7.93(1H,d,J=8.4Hz), 7.98(1H,s), 8.06(1H,d,J=8.4Hz), 8.13(2H,d,J=8.8Hz).

ESI-Mass; 334(MH^+).

Example 3 Synthesis of 1-(1-methylpiperazin-4-yl)-3-[4-(2-hydroxyethoxy)phenyl]isoquinoline

(3-1) 1-(1-Methylpiperazin-4-yl)-3-(4-hydroxyphenyl)isoquinoline

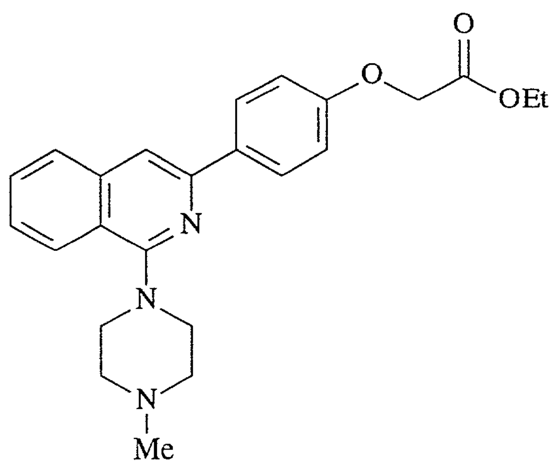


To 1-(1-methylpiperazin-4-yl)-3-(4-methoxy-1-phenyl)isoquinoline (2.07 g) was added 47% hydrobromic acid (28 ml), and the resulting mixture was heated under reflux for 6.5

hr. After the resulting solution was left for cooling, it was basified (pH=10) by adding 5N sodium hydroxide thereto, and then extracted with chloroform. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. Methanol was added thereto, and the insoluble matter was collected by filtration and dried, to give the title compound as a pale red solid (946 mg, yield; 50%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 2.28(3H,s), 2.60(4H,br-s), 3.40(4H,br-s), 6.85(2H,d,J=8.8Hz), 7.48(1H,dd,J=8Hz,7Hz), 7.63(1H,dd,J=8Hz,7Hz), 7.79(1H,s), 7.86(1H,d,J=8Hz), 8.00(1H,d,J=8Hz), 8.01(2H,d,J=8.8Hz), 9.62(1H,s).

(3-2) 1-(1-Methylpiperazin-4-yl)-3-[4-(ethoxycarbonylmethoxy)phenyl]isoquinoline

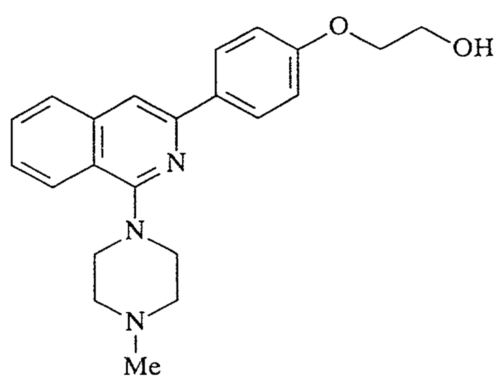


1-(1-Methylpiperazin-4-yl)-3-(4-hydroxy-1-phenyl)isoquinoline (320 mg) was dissolved in N,N-dimethylformamide (5 ml), to which was then added 60% sodium hydride (48 mg) under ice-cooling. The resulting mixture was stirred at room temperature for 1 hr. It was ice-cooled again,

to which was then added ethyl 2-bromoacetate (166 ml), for agitation for 6 hours. The reaction mixture was partitioned between ethyl acetate and water, and the resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the title compound as a pale yellow oil (171 mg, yield; 40 %).

^{1}H-NMR(400MHz, $CDCl_3$); δ (ppm) 1.31(3H,t,J=7.2Hz), 2.41(3H,s), 2.71(4H,t,J=4.4Hz), 3.56(4H,t,J=4.4Hz), 4.28(2H,q,J=7.2Hz), 4.67(2H,s), 7.01(2H,d,J=8.8Hz), 7.43(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.55(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.60(1H,s), 7.75(1H,d,8Hz), 8.04(1H,d,J=8Hz), 8.11(2H,d,8.8Hz).

<u>(3-3) 1-(1-Methylpiperazin-4-yl)-3-[4-(2-hydroxyethoxy)phenyl]isoquinoline</u>



1-(1-Methylpiperazin-4-yl)-3-[4-(ethoxycarbonylmethoxy)phenyl]isoquinoline (320 mg) was dissolved in tetrahydrofuran (5 ml), to which was added lithium aluminium hydride (16 mg) under ice-cooling, followed by stirring for 5 min. To the resulting reaction mixture were then added water (16 ml), 5N sodium hydroxide (16 ml) and water (48

ml) in this order. After diluting with ethyl acetate, it was filtered through Celite and evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), which was converted into a hydrochloride in a conventional manner, and then recrystallized from in ethanol, to give the hydrochloride of the title compound as yellow crystals (105 mg, yield; 50 %).

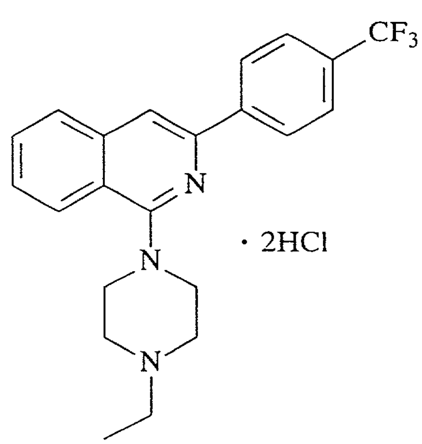
Hydrochloride:

m.p.; 131-133°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 2.85(3H,d,J=4.4Hz), 3.36(1H,t,J=11Hz), 3.38(1H,t,J=11Hz), 3.42(1H,t,J=12.6Hz), 3.45(1H,t,J=12.6Hz), 3.54(2H,d,J=11Hz), 3.73(2H,t,J=5Hz), 3.96(1H,d,J=12.6Hz), 4.04(2H,t,J=5Hz), 7.05(2H,d,J=8.8Hz), 7.55(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.70(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.93(1H,d,J=8Hz), 7.97(1H,s), 8.06(1H,d,J=8Hz), 8.12(2H,d,J=8.8Hz), 10.95(1H,br-s).

ESI-Mass; 364(MH^+).

Example 4 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(4-trifluoromethylphenyl)isoquinoline dihydrochloride



3-(4-Trifluoromethylphenyl)isoquinolin-1-one obtained by reacting N-methyl-o-toluamide (1.0 g) and 4-trifluoromethylbenzonitrile (1.15 g) according to Example 10-1 was added to phosphorous oxychloride (10 ml), and the resulting mixture was heated at 110°C for 3 hr. The reaction solution was evaporated, and ethyl acetate and water were added to the resulting residue. The resulting organic layer was washed with water, an aqueous solution of sodium bicarbonate and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting 1-chloro-3-(4-trifluoromethylphenyl)isoquinoline was reacted with N-ethylpiperazine (10 ml) at 120°C for 5 hr. The reaction solution was evaporated, and ethyl acetate and water were added to the resulting residue. The resulting organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the free compound of the title compound as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.6Hz,3H), 2.57(q,J=7.6Hz,2H), 2.78(m,4H), 3.60(m,4H), 7.50(br-t,1H), 7.62(br-t,1H), 7.71(d,J=8.4Hz,2H), 7.74(s,1H), 7.81(d,J=8.4Hz,1H), 8.09(br-d,1H), 8.26(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized

from ethanol/ether, to give 0.19 g of the title compound as a yellow powder.

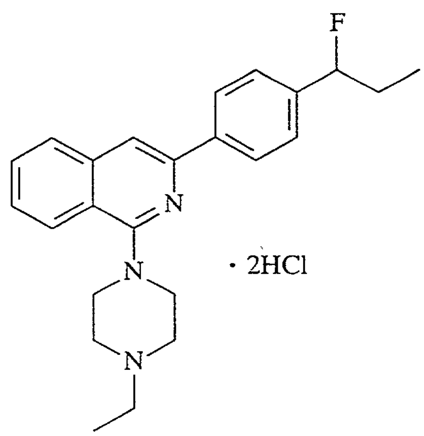
Hydrochloride:

m.p.; 131-133°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 3.19-3.27(m,2H), 3.30-3.41(m,2H), 3.52-3.65(m,4H), 4.02(br-d,2H), 7.67(ddd,J=8.4,7.2,1.2Hz,2H), 7.79(ddd,J=7.6,7.2,0.8Hz,1H), 7.88(d,J=8.4Hz,1H), 8.04(d,J=7.6Hz,1H), 8.16(d,J=8.4Hz,1H), 8.25(s,2H), 8.16(d,J=8.4Hz,1H), 11.27(br-s,1H).

MS(FAB) m/z 416$(M+H)^+$.

Example 5 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(1-fluoropropyl)phenyl]isoquinoline hydrochloride



Diethylaminosulfur trifluoride (0.27 g) was added to a solution of 1-(4-ethylpiperazin-1-yl)-3-[4-(1-hydroxypropyl)phenyl]isoquinoline (0.53 g) obtained in Example 19 in methylene chloride (30 ml) at -78 °C. After stirring the resulting mixture for 1 hr, it was returned to room temperature. An aqueous solution of saturated sodium bicarbonate and ethyl acetate were added to the resulting

reaction solution, for partitioning. The resulting organic layer was washed with water and brine, dried and concentrated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system) (0.38 g), and was then converted into a hydrochloride in a conventional manner, to give 0.36 g of the title compound as a yellow powder.

Free compound:

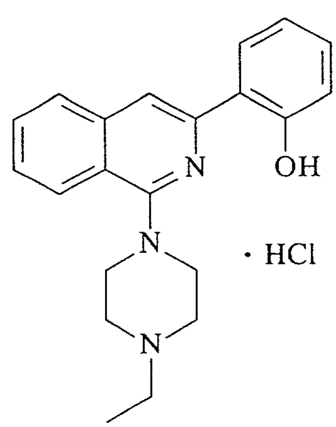
^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.01(t,J=7.2Hz,3H), 1.17(t,J=7.2Hz,3H), 1.82-2.10(m,2H), 2.56(q,J=7.2Hz,2H), 2.76(m,4H), 3.59(m,4H), 5.35-5.50(m,1H), 7.42(t,J=8.0Hz,2H), 7.45(t,J=8.0Hz,1H), 7.58(t,J=8.0Hz,2H), 7.68(s,1H), 7.79(d,J=8.0Hz,1H), 8.08(d,J=8.0Hz,1H), 8.17(d,J=8.0Hz,2H).

Hydrochloride:

m.p.; 147-149°C

MS(FAB) m/z 378(M+H)$^+$.

<u>Example 6 Synethesis of 1-(4-ethylpiperazin-1-yl)-3-(2-hydroxyphenyl)isoquinoline</u>



1-(4-Ethylpiperazin-1-yl)-3-(2-methoxyphenyl)isoquinoline (0.38 g) obtained in Example 8 was

dissolved in 48 % hydrobromic acid (15 ml) and reacted at 120°C for 1.5 hr. The reaction solution was evaporated to a final half volume, and then ice-cooled. The resulting precipitates were collected by filtration and washed with a small amount of ice-cold water. The resulting precipitates were treated with a 2N aqueous solutiong of sodium hydroxide. The resulting precipitates were collected by filtration, and washed with water and ether/n-hexane, to give 0.23 g of the free compound of the title compound. 70 mg of the free compound was converted into a hydrochloride in a conventional manner, to give 71 mg of the hydrochloride of the title compound title compound as a yellow powder.

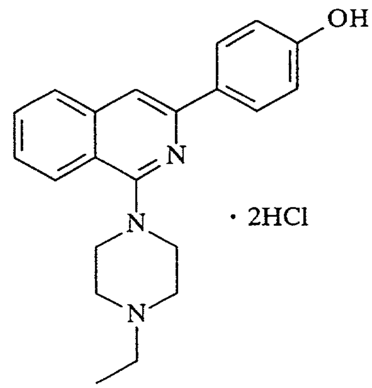
Hydrochloride:

m.p.; 228-230℃

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.31(t,J=7.2Hz,3H), 3.20-3.30(m,2H), 3.36-3.52(m,4H), 3.63-3.70(m,2H), 3.90-4.08(m,2H), 6.95(d,J=8.0Hz,2H), 6.95(t,J=8.0Hz,1H), 7.65(t,J=8.0Hz,2H), 7.80(t,J=8.0Hz,2H), 8.00-8.09(m,2H), 8.15(d,J=8.0Hz,2H), 8.27(s,1H).

MS(FAB) m/z 334$(M+H)^+$.

Example 7 Synethesis of 1-(4-ethylpiperazin-1-yl)-3-(4-hydroxyphenyl)isoquinoline



1-(4-Ethylpiperazin-1-yl)-3-(4-methoxyphenyl)isoquinoline (1.50 g) obtained in Example 10 was dissolved in 48 % hydrobromic acid (15 ml) and reacted at 120°C for 1.5 hr. The reaction solution was evaporated to a final half volume, and ice-cooled. The resulting precipitates were collected by filtration, and then washed with a small amount of ice-cold water. The precipitates were treated with a 2N aqueous solution of sodium hydroxide, followed by collecting the precipitates by filtration, washed with water and ether/n-hexane, and then dried in warm air, to give the title compound (1.08 g, yield; 75 %).

Free compound:

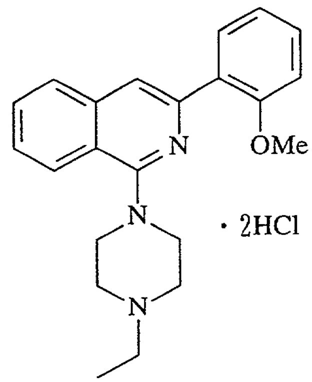
m.p.; 204-206°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.08(t,J=7.2Hz,3H), 2.38-2.52(m,2H), 2.68(br,4H), 3.42(br,4H), 6.87(d,J=8.8Hz,2H), 7.51(ddd,J=8.0,7.2,0.8Hz,1H), 6.87(ddd,J=8.0,7.2,0.8Hz,1H), 7.82(s,1H), 7.88(d,J=8.0Hz,1H), 8.02-8.06(m,1H), 8.03(d,J=8.8Hz,2H), 9.66(s,1H).

MS(FAB) m/z 334(M+H)$^+$.

Example 8 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(2-

methoxyphenyl)isoquinoline dihydrochloride



To 3-(2-methoxyphenyl)isoquinolin-1-one obtained by reacting N-methyl-o-toluamide (2.30 g) and 2-methoxybenzonitrile (2.0 g) according to Example 10-1 was added phosphorous oxychloride (10 ml), and the resulting mixture was heated at 100 °C for 2 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water, for partitioning. The resulting organic layer was washed with water, an aqueous solution of sodium bicarbonate and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting 1-chloro-3-(2-methoxyphenyl)isoquinoline was reacted with N-ethylpiperazine (10 ml) at 120°C for 8 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the free compound of the title compound as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=8.0Hz,3H), 2.56(q,J=8.0Hz,2H), 2.75(m,4H), 3.55(m,4H), 3.93(s,3H), 7.02(d,J=9.4Hz,1H), 7.10(t,J=9.4Hz,1H), 7.32(br-t,1H), 7.45(t,J=9.4Hz,1H), 7.58(t,J=9.2Hz,1H), 7.78(d,J=9.2Hz,1H), 7.98(s,1H), 8.08(d,J=9.2Hz,1H), 8.15(d,J=4.5Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 0.42 g of the title compound as a yellow powder.

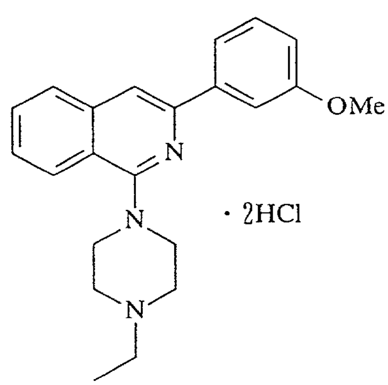
Hydrochloride:

m.p.; 133-135℃

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 3.19-3.26(m,2H), 3.29-3.41(m,2H), 3.53-3.65(m,4H), 3.90(s,3H), 3.97(br-d,2H), 7.11(br-t,1H), 7.19(d,J=8.0Hz,1H), 7.42(br-t,1H), 7.65(br-t,1H), 7.78(br-t,1H), 7.98(d,J=8.0Hz,2H), 8.06(s,1H), 8.15(d,J=8.8Hz,1H), 11.30(br-s,1H).

MS(FAB) m/z 348$(M+H)^+$.

<u>Example 9 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(3-methoxyphenyl)isoquinoline dihydrochloride</u>



3-(4-Methoxyphenyl)isoquinolin-1-one obtained by

reacting N-methyl-o-toluamide (1.49 g) and 3-methoxybenzonitrile (1.33 g) according to Example 10-1 was reacted with phosphorous oxychloride (10 ml) according to Example 10-2, to give 1-chloro-3-(3-methoxyphenyl)isoquinoline. Then, it was reacted with N-ethylpiperazine (10 ml) at 120°C for 6 hr. The reaction solution was evaporated, and ethyl acetate and water were added to the resulting residue. The resulting organic layer was washed with water and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the free compound of the title compound as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.6Hz,3H), 2.55(q,J=7.6Hz,2H), 2.76(m,4H), 3.58(m,4H), 3.90(s,3H), 6.93(dd,J=8.4,2.4Hz,1H), 7.37(t,J=8.4Hz,1H), 7.45(br-t,1H), 7.59(br-t,1H), 7.69(s,1H), 7.70-7.75(m,1H), 7.77-7.82(m,2H), 8.17(d,J=8.0Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner and recrystallized from ethanol/ether, to give 0.27 g of the title compound as a yellow powder.

Hydrochloride:

m.p.; 108-110°C

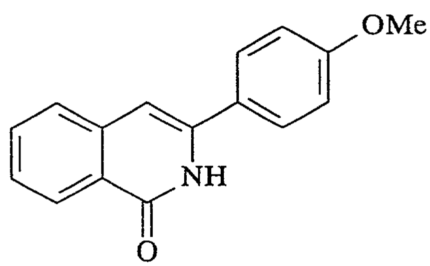
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 3.18-

3.27(m,2H), 3.35(q,J=7.2Hz,2H), 3.52-3.66(m,4H), 3.87(s,3H), 3.96-4.04(m,2H), 7.01(br-d,1H), 7.44(t,J=8.0Hz,1H), 7.63(br-t,1H), 7.73-7.82(m,3H), 8.10(d,J=8.0Hz,1H), 8.13(s,1H), 8.13(d,J=8.4Hz,1H), 11.25(br-s,1H).

MS(FAB) m/z 348$(M+H)^+$.

Example 10 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(4-methoxyphenyl)isoquinoline

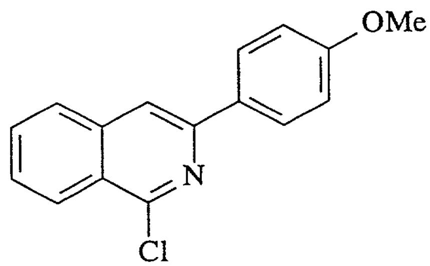
(10-1) 3-(4-Methoxyphenyl)isoquinolin-1-one



To a solution of N-methyl-o-toluamide (4.47 g) in THF (100 ml) was added dropwise 1.6 M n-BuLi (40 ml, 2.2 equivalents) in nitrogen atmosphere at 0 °C. After stirring for 2 hr, the resulting solution was cooled in a dry ice/acetone bath to -70 °C, followed by the addition of anisole (4.0 g) at once. The reaction mixture was drawn out of the dry ice/acetone bath, and then returned to room temperature. Three hours later, an aqueous solution of saturated ammonium chloride and ether were added thereto, which was stirred for further 1 hr. The resulting white precipitates were collected by filtration, and then washed with water, ether and n-hexane, in this order. The resulting precipitates were dried, to give the title compound (1.72 g, yield; 24%).

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 3.84(s,3H), 6.85(s,1H), 7.05(d,J=8.4Hz,2H), 7.46(m,1H), 7.69(s,1H), 7.65-7.72(m,1H), 7.78(d,J=8.4Hz,2H), 8.20(d,J=8.0Hz,1H).

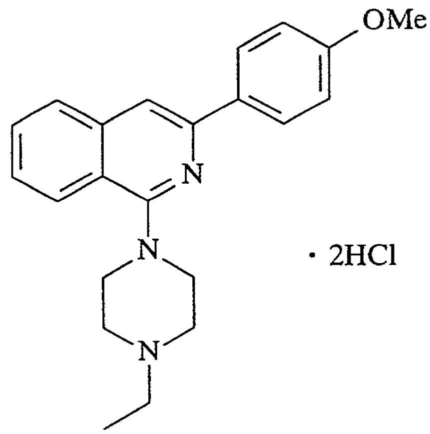
(10-2) 1-Chloro-3-(4-methoxyphenyl)isoquinoline



3-(4-Methoxyphenyl)isoquinolin-1-one (1.70 g) was added to phosphorus oxychloride (10 ml), and the resulting mixture was heated at 110 °C for 3 hr. The reaction mixture was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water, an aqueous solution of sodium bicarbonate and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a white powder (1.76 g, yield; 96%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 3.87(s,3H), 7.02(d,J=8.4Hz,2H), 7.61(br-t,1H), 7.71(br-t,1H), 7.84(d,J=8.0Hz,1H), 7.92(s,1H), 8.07(d,J=8.4Hz,2H), 8.32(d,J=8.0Hz,1H).

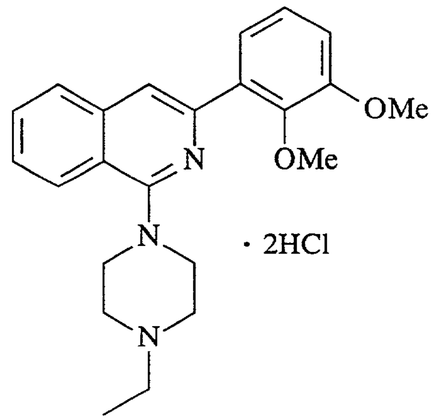
(10-3) 1-(4-Ethylpiperazin-1-yl)-3-(4-methoxyphenyl)isoquinoline



A mixture of 1-chloro-3-(4-methoxyphenyl)isoquinoline (0.89 g), N-ethylpiperazine (0.86 g) and potassium carbonate (1.10 g) was heated in dimethylformamide (20 ml) at 90°C for 12 hr. The reaction mixture was evaporated, water was added to the resulting residue, and then it was extracted with ethyl acetate. The resulting organic layer was washed with water and brine, dried over magnesium sulfate, and then the solvent was romoved. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the tilte compound as a pale brown oil (1.02 g, yield; 88%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.76(br,4H), 3.59(br,4H), 3.87(s,3H), 7.00(d,J=8.4Hz,2H), 7.43(t,J=8.0Hz,1H), 7.56(t,J=8.0Hz,1H), 7.61(s,1H), 7.76(d,J=8.0Hz,1H), 8.06(d,J=8.0Hz,1H), 8.12(d,J=8.4Hz,2H).

Example 11 Synthesis of 3-(2,3-dimethoxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline dihydrochloride



3-(2,3-Dimethoxyphenyl)isoquinolin-1-one obtained by reacting N-methyl-o-toluamide (1.49 g) and 2,3-dimethoxybenzonitrile (1.63 g) according to Example 10-1 was added to phosphorous oxychloride (10 ml), and the resulting mixture was heated at 110 °C for 3 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water, an aqueous solution of sodium bicarbonate and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting 1-chloro-3-(2,3-dimethoxyphenyl)isoquinoline was reacted with N-ethylpiperazine (15 ml) at 120°C for 5 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water and brine, and was then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the free compound of the title compound as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.76(m,4H), 3.55(m,4H), 3.78(s,3H), 3.92(s,3H), 6.94(d,J=7.5Hz,1H), 7.16(t,J=7.5Hz,2H), 7.47(dt,J=7.6,1.2Hz,1H), 7.56-7.19(m,2H), 7.78(d,J=7.6Hz,2H), 7.96(s,1H), 8.10(d,J=7.6Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 0.19 g of the title compound as a yellow powder.

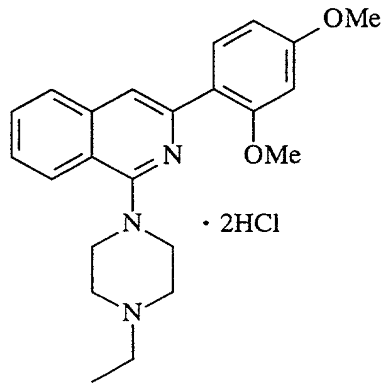
Hydrochloride:

m.p.; 122-123°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 3.18-3.27(m,2H), 3.35(q,J=7.2Hz,2H), 3.53(br-t,2H), 3.62(br-d,2H), 3.74(s,3H), 3.88(s,3H), 3.94(br-d,2H), 7.14(dd,J=8.0,1.6Hz,1H), 7.20(t,J=8.0Hz,1H), 7.49(dd,J=8.4,1.6Hz,1H), 7.65(t,J=7.2Hz,1H), 7.77(t,J=7.2Hz,1H), 7.97(s,1H), 8.00(d,J=8.4Hz,1H), 8.15(d,J=8.4Hz,1H), 11.19(br-s,1H).

MS(FAB) m/z 378$(M+H)^+$.

Example 12 Synthesis of 3-(2,4-dimethoxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline dihydrochloride



Phosphorous oxychloride (10 ml) was added to 3-(2,4-dimethoxyphenyl)isoquinolin-1-one obtained by reacting N-methyl-o-toluamide (2.20 g) and 2,4-dimethoxybenzonitrile (2.40 g) according to Example 10-1, and the resulting mixture was heated at 100°C for 1 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water, an aqueous solution of sodium bicarbonate and brine, and was then dried over magnesium sulfate. The solvent was evaporated, and the resulting 1-chloro-3-(2,4-dimethoxyphenyl)isoquinoline was reacted with N-ethylpiperazine (15 ml) at 110°C for 12 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water and brine, and was then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the free compound of the title compound as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,CDCl$_3$); δ (ppm) 1.15(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.70(m,4H), 3.55(m,4H), 3.85(s,3H), 3.91(s,3H), 6.57(d,J=4.0Hz,1H), 6.64(dd,J=8.8,4.0Hz,1H), 7.43(t,J=8.0Hz,1H), 7.56(t,J=8.0Hz,1H), 7.77(d,J=8.0Hz,1H), 7.95(s,1H), 8.04(d,J=8.0Hz,1H), 8.13(d,J=8.8Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 0.12 g of the title compound as a yellow powder.

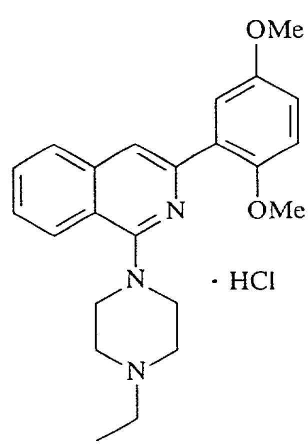
Hydrochloride:

m.p.; 145-148°C

^{1}H-NMR(400MHz,DMSO-d$_6$); δ (ppm) 1.36(t,J=7.4Hz,3H), 3.35(q,J=7.4Hz,2H), 3.44-3.55(m,2H), 3.64-3.75(m,2H), 3.77-3.88(m,2H), 3.84(s,3H), 3.86(s,3H), 4.17-4.26(m,2H), 6.66(br-s,1H), 6.67-6.82(m,1H), 7.57(dd,J=8.4,1.2Hz,1H), 7.66-7.74(m,2H), 7.88-7.84(m,2H), 8.08(br-d,1H).

MS(FAB) m/z 378(M+H)$^+$.

<u>Example 13 Synthesis of 3-(2,5-dimethoxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline dihydrochloride</u>



3-(2,5-Dimethoxyphenyl)isoquinolin-1-one (0.61 g) obtained by reacting N-methyl-o-toluamide (1.64 g) and 2,5-dimethoxybenzonitrile (1.80 g) according to Example 10-1 was reacted with phosphorous oxychloride (10 ml) according to Example 10-2, to give 1-chloro-3-(2,5-dimethoxyphenyl)isoquinoline, which was then reacted with N-ethylpiperazine (15 ml) at 100°C for 8 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the free compound of the title compound as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.76(m,4H), 3.55(m,4H), 3.86(s,3H), 3.88(s,3H), 6.88(dd,J=8.1,2.4Hz,1H), 6.96(t,J=8.1Hz,1H), 7.46(br-t,1H), 7.57(br-t,1H), 7.76-7.84(m,1H), 8.04(s,1H), 8.08(s,1H), 8.12(d,J=8.0Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 0.55 g of the title compound as a yellow powder.

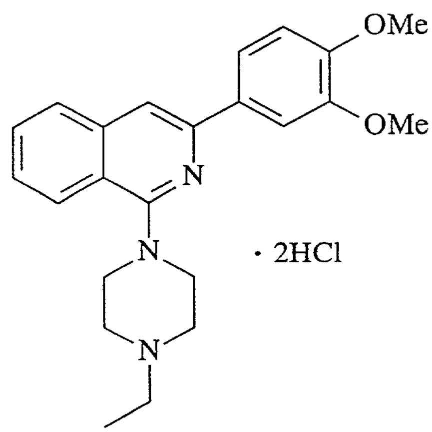
Hydrochloride:

m.p.; 189-191°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.32(t,J=7.2Hz,3H), 3.19-3.28(m,2H), 3.36(q,J=7.2Hz,2H), 3.48(br-t,2H), 3.63(br-d,2H), 3.79(s,3H), 3.86(s,3H), 3.97(br-d,2H), 6.98(dd,J=8.0,3.2Hz,1H), 7.12(d,J=9.2Hz,1H), 7.61-7.66(m,2H), 7.51(t,J=7.2Hz,1H), 7.97(d,J=8.4Hz,1H), 8.12(s,1H), 8.11-8.16(m,1H), 10.73(br-s,1H).

MS(FAB) m/z 378(M+H)$^+$.

Example 14 Synthesis of 3-(3,4-dimethoxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline dihydrochloride



3-(3,4-Dimethoxyphenyl)isoquinolin-1-one (0.98 g) obtained by reacting N-methyl-o-toluamide (2.60 g) and 3,4-dimethoxybenzonitrile (2.83 g) according to Example 10-1 was reacted with phosphorous oxychloride (15 ml) at 80°C for 3 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water, an aqueous solution of sodium bicarbonate and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting 1-chloro-3-(3,4-dimethoxyphenyl)isoquinoline was reacted with

N-ethylpiperazine (15 ml) at 100°C for 5 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the free compound of the title compound as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.19(t,J=7.2Hz,3H), 2.78(m,4H), 3.59(m,4H), 3.95(s,3H), 4.01(s,3H), 6.98(d,J=8.4Hz,1H), 7.45(ddd,J=8.0,7.2,1.2Hz,1H), 7.58(ddd,J=8.0,7.2,1.2Hz,1H), 7.64(s,1H), 7.72(dd,J=8.4,2.0Hz,1H), 7.78(br-d,J=8.0Hz,1H), 7.84(d,J=2.0Hz,1H), 8.07(br-d,J=8.0Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 1.38 g of the title compound as a yellow powder.

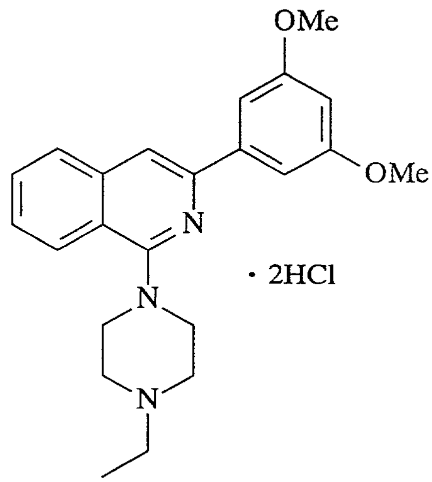
Hydrochloride:

m.p.; 125-126.5°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.6Hz,3H), 3.27(q,J=7.6Hz,2H), 3.30(br-t,2H), 3.45(br-t,2H), 3.68(br-d,2H), 3.74(s,3H), 3.78(s,3H), 3.98(br-d,2H), 6.83(d,J=8.4Hz,1H), 7.06(dd,J=8.0,2.0Hz,1H), 7.09(d,J=2.0Hz,1H), 7.29(s,1H), 7.59(br-t,1H), 7.65(br-d,1H), 7.76(br-t,2H), 7.90(br-d,1H).

MS(FAB) m/z 378$(M+H)^+$.

Example 15 Synthesis of 3-(3,5-dimethoxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline dihydrochloride



3-(3,5-Dimethoxyphenyl)isoquinolin-1-one obtained by reacting N-methyl-o-toluamide (1.49 g) and 3,5-dimethoxybenzonitrile (1.63 g) according to Example 10-1 was added to phosphorous oxychloride (10 ml), and the resulting mixture was heated at 100°C for 3 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water, an aqueous solution of sodium bicarbonate and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting 1-chloro-3-(3,5-dimethoxyphenyl)isoquinoline was reacted with N-ethylpiperazine (15 ml) at 120°C for 4 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water and brine, and then dried over magnesium sulfate.

The solvent was evaporated, and the reuslting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the free compound of the title compound as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz, $CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.77(m,4H), 3.58(m,4H), 3.90(s,3H), 6.51(d,J=2.4Hz,1H), 7.35(br-d,2H), 7.45(br-t,1H), 7.59(br-t,1H), 7.67(s,1H), 7.79(d,J=7.6Hz,2H), 8.07(d,J=7.6Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 0.51 g of the title compound as a yellow powder.

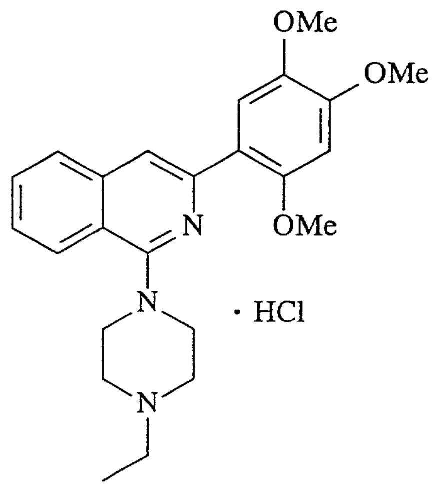
Hydrochloride:

m.p.; 121-123°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.32(t,J=7.2Hz,3H), 3.18-3.27(m,2H), 3.34(q,J=7.2Hz,2H), 3.48-3.58(m,2H), 3.63(br-d,2H), 3.85(s,3H), 4.00(br-d,2H), 6.57(dd,J=2.4Hz,1H), 7.44(dx2,J=2.4Hz,2H), 7.62(br-t,1H), 7.62(br-t,1H), 8.00(br-d,1H), 8.12(br-d,1H), 8.14(s,1H), 11.02(br-s,1H).

MS(FAB) m/z 378$(M+H)^+$.

Example 16 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(2,4,5-trimethoxyphenyl)isoquinoline dihydrochloride



3-(2,4,5-Trimethoxyphenyl)isoquinolin-1-one obtained by reacting N-methyl-o-toluamide (1.50 g) and 2,4,5-trimethoxybenzonitrile (1.93 g) according to Example 10-1 was reacted with phosphorous oxychloride (10 ml) according to Example 10-2, to give 1-chloro-3-(2,4,5-trimethoxyphenyl)isoquinoline, which was then reacted with N-ethylpiperazine (15 ml) at 120°C for 5 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was wahsed with water and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the reuslting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the free compound of the title compound as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.76(m,4H), 3.55(m,4H), 3.88(s,3H), 3.91(s,3H), 3.94(s,3H), 6.65(s,1H), 7.43(t,J=8.0Hz,1H),

7.56(t,J=8.0Hz,1H), 7.77(d,J=8.0Hz,1H), 7.92(s,1H), 8.03(s,1H), 8.06(d,J=8.0Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/ether, to give 0.23 g of the title compound as a yellow powder.

Hydrochloride:

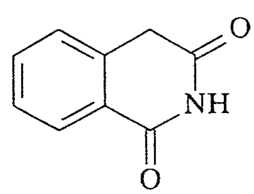
m.p.; 158-160°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.32(t,J=7.2Hz,3H), 3.18-3.27(m,2H), 3.35(q,J=7.2Hz,2H), 3.52(br-t,2H), 3.63(br-d,2H), 3.80(s,3H), 3.88(s,3H), 3.92(s,3H), 3.99(br-d,2H), 6.84(s,1H), 7.59(br-t,1H), 7.71-7.78(m,2H), 7.76(s,1H), 7.94(d,J=8.0Hz,1H), 8.10(s,1H), 8.08-8.13(m,1H), 10.76(br-s,1H).

MS(FAB) m/z 408(M+H)$^+$.

Example 17 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(4-hydroxymethylphenyl)isoquinoline hydrochloride

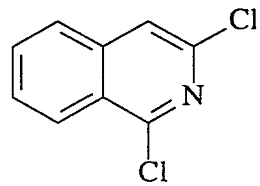
(17-1) Homophthalimide



Homophthalic anhydride (20 g) and urea (60 g) were reacted at 170°C for 1 hr. The reaction mixture was cooled, water (500 ml) was added thereto, and then the resulting precipitates were collected by filtration. The precipitate were washed with water and dried in hot air, to give 10.5 g of homophthalimide

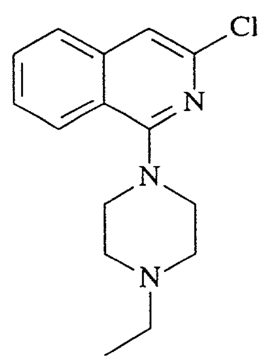
as a white powder.

(17-2) 1,3-Dichloroisoquinoline



A mixture solution of homophthalimide (10.5 g) and phenylphosphonate dichloride (30 ml) was heated at 110°C for 2 hr. After the reaction mixture was cooled, water was added thereto, and then the resulting mixture was neutralized with sodium carbonate. The resulting mixture was extracted with ethyl acetate, washed with brine, dried, and then the solvent was evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride), to give 9.30 g of the title compound as white crystals.

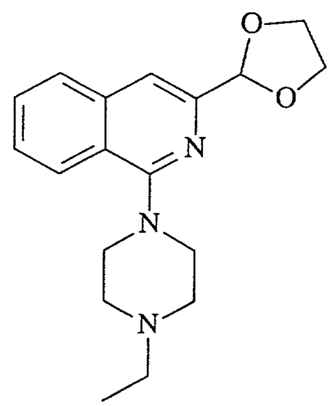
(17-3) 3-Chloro-1-(4-ethylpiperazin-1-yl)isoquinoline



1,3-Dichloroisoquinoline (9.30 g), N-ethylpiperazine (5.90 g) and potassium carbonate (10.0 g) were reacted in dimethylformamide (70 ml) at 70°C for 5 hr. The reaction solution was evaporated and partitioned between ethyl acetate and water. The resulting organic phase was washed with water,

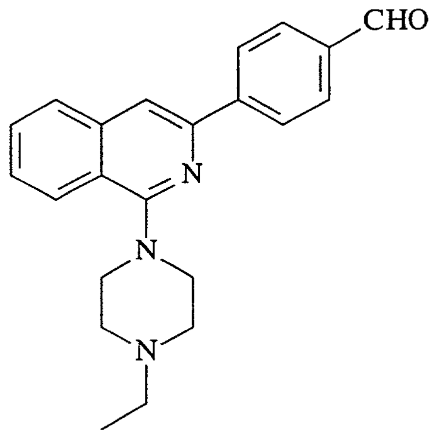
dried and evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 12.80 g of the title compound as a pale brown oil.

(17-4) 3-[(1,3-Dioxolan-2-yl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline



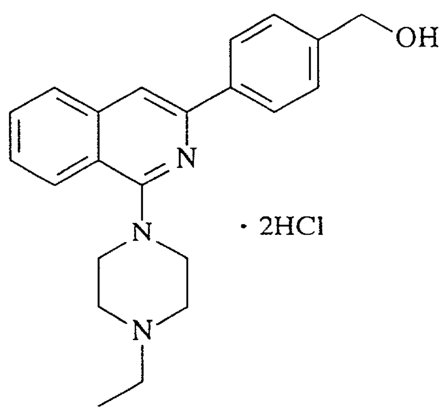
3-Chloro-1-(4-ethylpiperazin-1-yl)isoquinoline (3.5 g) and 4-(1,3,2-dioxaborynan-2-yl)-1-(1,3-dioxolan-2-yl)benzene (5.0 g) were reacted in dimethylformamide (50 ml), in the presence of cesium carbonate (7.3 g) and tetrakistriphenylphosphinepalladium (0.3 g) at 80°C in a nitrogen stream for 12 hr. The reaction solution was evaporated, and then partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 4.66 g of the title compound as a pale yellow oil.

(17-5) 1-(4-Ethylpiperazin-1-yl)-3-(4-formylphenyl)isoquinoline



3-[(1,3-Dioxolan-2-yl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline (4.50 g) was dissolved in methanol (50 ml), a 1N hydrochloric acid (50 ml) was added thereto, and then the mixture was reacted at 50°C for 1 hr. The reaction solution was evaporated, basified with sodium carbonate, and extracted with ethyl acetate. The resulting organic layer was washed with water and brine in this order, dried and concentrated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 3.62 g of the title compound as a pale yellow oil.

<u>(17-6) 1-(4-Ethylpiperazin-1-yl)-3-(4-hydroxymethylphenyl)isoquinoline hydrochloride</u>



Sodium tetrahydroboride (0.20 g) was added to a solution of 1-(4-ethylpiperazin-1-yl)-3-(4-formylphenyl)isoquinoline (0.35g) in methanol (20 ml) at 0°C. The reaction solution was stirred for 30 min and then concentrated. Water was added to the resulting residue, and then extracted with methylene chloride. The resulting product was dried and concentrated. The resulting residue was purified by NH-silica gel column chromatography (ethyl acetate), to give the free compound of the title compound as a pale yellow oil. The free form was converted into a hydrochloride in a conventional manner, to give 0.21 g of the title compound as a yellow powder.

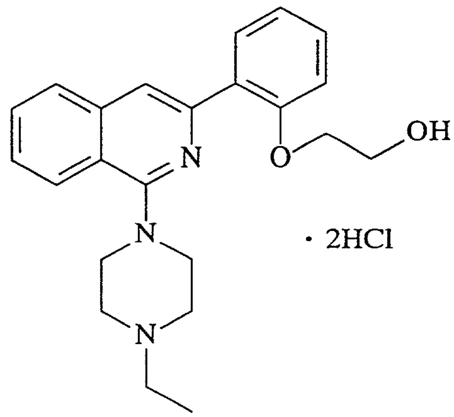
Hydrochloride:

m.p.; 145-147℃

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 3.17-3.27(m,2H), 3.29-3.41(m,2H), 3.50-3.66(m,4H), 3.99(d,J=9.2Hz,2H), 4.57(s,2H), 7.45(d,J=8.0Hz,2H), 7.57-7.63(m,1H), 7.71-7.77(m,1H), 7.99(d,J=8.0Hz,1H), 8.08(s,1H), 8.12(d,J=8.0Hz,1H), 8.17(d,J=8.0Hz,2H), 11.18(m,1H).

MS(FAB) m/z 348(M+H)$^+$.

Example 18 Synthesis of 3-[2-(2-hydroxyethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners as in Examples 161-2 and then 20, an oil was obtained from 1-bromo-2-(2-benzyloxyethoxy)benzene (886 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (904 mg). Methanol (30 ml) and a palladium/carbon catalyst (200 mg) were added to the oil, which was then reacted in hydrogen atmosphere overnight at room temperature. Thereafter, the reaction solution was filtered through Celite and evaporated. The resulting residue was basified with a 1N aqueous solution of sodium hydroxide, and extracted with ethyl acetate. The resulting organic layer was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography, to give an oil. The oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals (733 mg, yield; 89%).

Hydrochloride:

m.p.; 158-160℃

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 3.18-3.28(m,2H), 3.32-3.42(m,2H), 3.55-3.63(m,4H), 3.79-

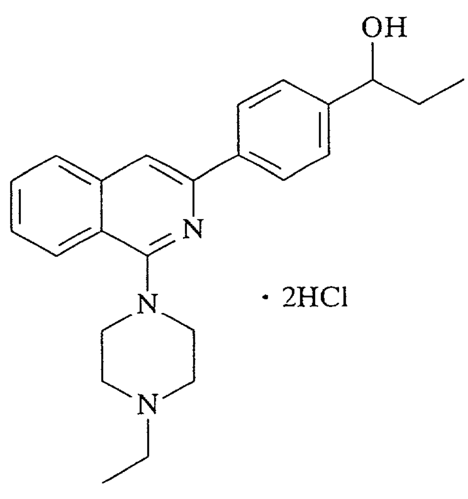
3.82(m,2H), 4.00(d,J=14.0Hz,2H), 4.14-4.16(m,2H), 7.11(t,J=8.4Hz,1H), 7.18(d,J=8.4Hz,1H), 7.39(dt,J=8.4,1.6Hz,1H), 7.64(t,J=8.0Hz,1H), 7.78(t,J=8.0Hz,1H), 7.95(d,J=8.0Hz,1H), 8.05(d,J=8.4Hz,1H), 8.15(d,J=8.0Hz,1H), 8.29(s,1H).

MS(FAB) m/z 378$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 2.54(q,J=7.2Hz,2H), 2.74(br,4H), 3.53(br,4H), 3.92(d,J=4.4Hz,2H), 4.21(d,J=4.4Hz,2H), 7.03(d,J=8.0Hz,1H), 7.11(dt,J=8.0,1.2Hz,1H), 7.33(dt,J=8.0,1.6Hz,1H), 7.48(ddd,J=8.4,8.0,1.2Hz,1H), 7.59(ddd,J=8.4,8.0,1.2Hz,1H), 7.75(d,J=8.0Hz,1H), 7.81(s,1H), 7.91(dd,J=8.0,1.6Hz,1H), 8.10(d,J=8.4Hz,1H).

<u>Example 19 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(1-hydroxypropyl)phenyl]isoquinoline hydrochloride</u>



To a solution of 1-(4-ethylpiperazin-1-yl)-3-(4-formylphenyl)isoquinoline (1.20 g) obtained in Example 17-5 in

tetrahydrofuran (60 ml) was added 3M ethylmagnesium bromide/diethyl ether solution (2.0 ml) at 0 °C, and the mixture was stirred for 2 hr. To the resulting reaction solution were added a 2N aqueous solution of hydrochloric acid (20 ml) and ethyl acetate. The resulting aqueous layer was basified with a 2N aqueous solution of sodium hydroxide, and extracted with ethyl acetate. The resulting organic layer was washed with water and brine, dried and concentrated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 1.03 g of the free compound of the title compound. 0.50 g of the resulting free compound was converted into a hydrochloride in a conventional manner, to give 0.48 g of the title compound as a yellow powder.

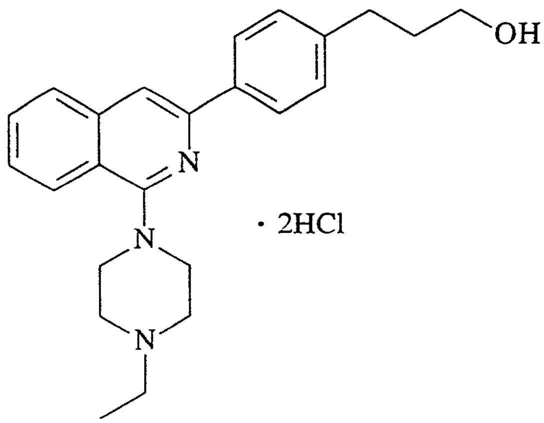
Hydrochloride:

m.p.; 143-144°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.86(t,J=7.2Hz,3H), 1.34(t,J=7.2Hz,3H), 1.66(m,2H), 3.18-3.28(m,2H), 3.29-3.41(m,2H), 3.49-3.66(m,4H), 3.95-4.04(m,2H), 4.52(t,J=6.4Hz,1H), 7.44(d,J=8.4Hz,2H), 7.58-7.64(m,1H), 7.71-7.77(m,1H), 7.98(d,J=8.0Hz,1H), 8.07(s,1H), 8.11(d,J=8.4Hz,1H), 8.15(d,J=8.4Hz,2H), 11.23(m,1H).

MS(FAB) m/z 376(M+H)$^+$.

<u>Example 20 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxypropyl)phenyl]isoquinoline hydrochloride</u>



[4-(2-Ethoxycarbonylethyl)phenyl]tributylstannum (2.998 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.292 g) were reacted in the presence of tetrakistriphenylphosphine (0.185 g) in xylene (20 ml) in nitrogen atmosphere for 2 hr. After cooling, the reaction solution was filtered. The resulting filtrate was extracted with a 5N aqueous solution of hydrochloric acid. The resulting aqueous layer was basified with a 5N sodium hydroxide and extracted with ethyl acetate. The resulting organic layer was washed with water and brine, dried and concentrated. The resulting 1-(4-ethylpiperazin-1-yl)-3-[4-(2-ethoxycarbonylethyl)phenyl]isoquinoline was dissolved in tetrahydrofuran (20 ml), and then added dropwise into a suspension of lithium aluminium hydride (0.106 g). The reaction solution was stirred at room temperature for 3 hr. After cooling, water and an aqueous solution of sodium hydroxide and water were added thereto in this order, and the resulting mixture was stirred at room temperature for 1 hr. The resulting precipitates were filtered off, and the residue washed with

ethyl acetate. The filtrate was concentrated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.527 g of 1-(4-ethylpiperazin-1-yl)-3-[4-(1-hydroxypropyl)phenyl]isoquinoline as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.91-1.98(m,2H), 2.56(q,J=7.2Hz,2H), 2.76-2.79(m,6H), 3.59(br-t,4H), 3.71(t,J=6.4Hz,2H), 7.31(d,J=8.0Hz,2H), 7.45(br-t,1H), 7.58(br-t,1H), 7.67(s,1H), 7.78(d,J=8.0Hz,1H), 8.07(d,J=7.6Hz,1H), 8.10(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a a conventional manner, to give the title compound as a yellow powder.

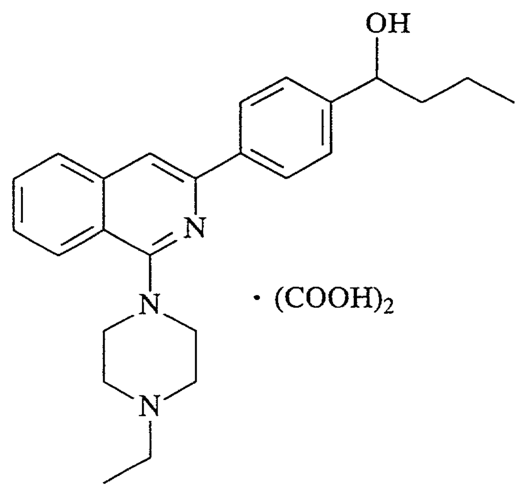
Hydrochloride:

m.p.; 116-119°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 1.73-1.80(m,2H), 2.68(t,J=7.8Hz,2H), 3.20-3.27(m,2H), 3.31-3.39(m,2H), 3.45(t,J=6.6Hz,2H), 3.52(br-t,2H), 3.62(br-d,2H), 4.00(br-d,2H), 7.34(d,J=8.0Hz,2H), 7.60(br-t,1H), 7.74(br-t,1H), 7.98(d,J=8.0Hz,1H), 8.05(s,1H), 8.11(d,J=8.4Hz,2H), 10.95(br-s,1H).

MS(FAB) m/z 376$(M+H)^+$.

Example 21 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(1-hydroxybutyl)phenyl]isoquinoline oxalate



(4-Butyrylphenyl)tributylstannum (1.566 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.985 g) was reacted in the presence of tetrakistriphenylphosphine (0.138 g) in xylene (20 ml) in nitrogen atmosphere for 2 hr. After cooling, the reaction solution was filtered. The resulting filtrate was extracted with a 5N aqueous solution of hydrochloric acid. The resulting aqueous layer was basified with 5N sodium hydroxide, and then extracted with ethyl acetate. The resulting organic layer was washed with water and brine, dried and concentrated. The resulting 1-(4-ethylpiperazin-1-yl)-3-(4-butyrylphenyl)isoquinoline (0.177 g) was dissolved in methanol, and then excess amount of sodium borohydride in was added thereto little by little. After the completion of the reaction was confirmed, the solvent was evaporated. To the resulting residue was added water, and then extracted with ethyl acetate. The resulting product was washed with brine, dried over magnesium sulfate, and then the solvent was evaporated. The resulting residue was purified by silica gel column

chromatography (methylene chloride/methanol system), to give 0.150 g of the title compound as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ(ppm) 0.95(t,J=7.2Hz,3H), 1.18(t,J=7.2Hz,3H), 1.31-1.62(m,2H), 1.69-1.89(m,2H), 2.57(q,J=7.2Hz,2H), 2.77(br-s,4H), 3.60(br-s,4H), 4.76(t,J=6.8Hz,1H), 7.44-7.48(m,3H), 7.59(br-t,1H), 7.70(s,1H), 7.80(d,J=7.6Hz,1H), 8.08(d,J=8.0Hz,1H), 8.17(d,J=8.4Hz,2H).

The resulting compound was converted into an oxalate in a conventional manner, to give the title compound as a white powder.

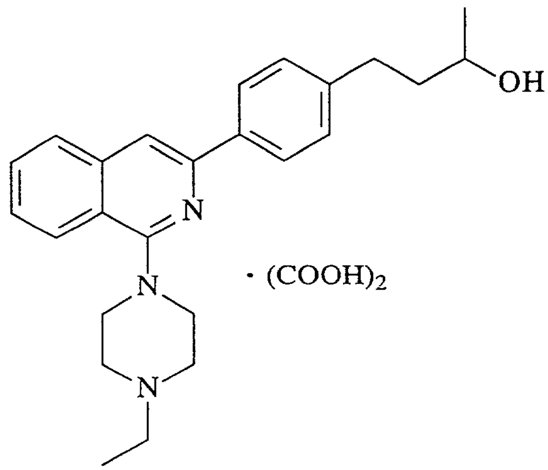
Oxalate:

m.p.; 198.5-199.5°C

^{1}H-NMR(400MHz,DMSO-d_6); δ(ppm) 0.89(t,J=7.2Hz,3H), 1.26(t,J=7.2Hz,3H), 1.22-1.42(m,2H), 1.53-1.69(m,2H), 3.12(br-q,2H), 3.36(br-s,4H), 3.67(br-s,4H), 4.59(t,J=6.4Hz,1H), 7.44(d,J=8.4Hz,2H), 7.60(br-t,1H), 7.73(br-t,1H), 7.98(d,J=7.6Hz,1H), 8.05(s,1H), 8.10-8.15(m,3H).

MS(FAB) m/z 390$(M+H)^+$.

<u>Example 22 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxybutyl)phenyl]isoquinoline oxalate</u>



[4-(3-Oxobutyl)phenyl]tributylstannum (2.457 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.405 g) were reacted in the presence of tetrakistriphenylphosphine (0.217 g) in xylene (20 ml) in nitrogen atmosphere for 2 hr. After cooling, the reaction solution was filtered. The resulting filtrate was extracted with a 5N aqueous solution of hydrochloric acid. The resulting aqueous layer was basified with 5N sodium hydroxide, and extracted with ethyl acetate. The resulting organic layer was washed with water and brine, dried and concentrated. The resulting 1-(4-ethylpiperazin-1-yl)-3-[4-(3-ethoxycarbonylpropyl)phenyl]isoquinoline was dissolved in methanol, which was then treated with excessive sodium borohydride. The reaction solution was concentrated, extracted with ethyl acetate, washed with water and brine, dried and then the solvent was removed. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.346 g of the title compound as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.25(d,J=6.4Hz,3H), 1.79-1.85(m,2H), 2.56(q,J=7.2Hz,2H), 2.70-2.86(m,6H), 3.59(br-t,4H), 3.87(tq,J=6.4Hz,1H), 7.31(d,J=8.0Hz,2H), 7.45(br-t,1H), 7.58(br-t,1H), 7.67(s,1H), 7.78(J=8.0Hz,1H), 8.06-8.11(m,3H).

The resulting compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as a white powder.

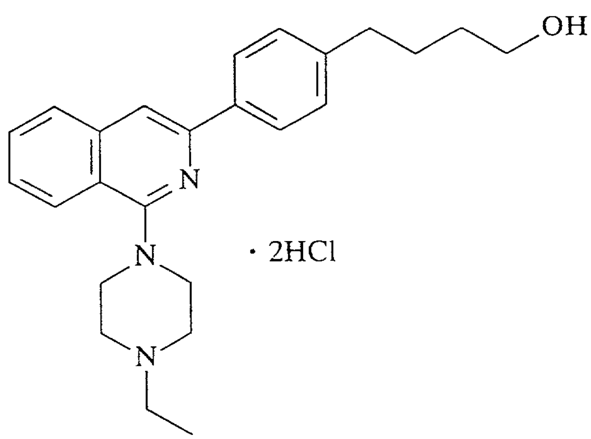
Oxalate:

m.p.; 193-194°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.10(d,J=6.0Hz,3H), 1.26(t,J=7.2Hz,3H), 1.62-1.69(m,2H), 2.60-2.77(m,2H), 3.11(br-q,2H), 3.35(br-s,4H), 3.58-3.66(m,5H), 7.33(d,J=8.4Hz,2H), 7.59(br-t,1H), 7.73(br-t,1H), 7.97(d,J=8.0Hz,1H), 8.03(s,1H), 8.10(d,J=8.4Hz,2H).

MS(FAB) m/z 390$(M+H)^+$.

Example 23 Synthesis of 3-[4-(4-hydroxybutyl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manner as in Example 20, an oil was obtained from 1-bromo-4-(4-acetoxybutyl)benzene (1.57 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.0 g). Methanol (15 ml) and a 1N aqueous solution of sodium hydroxide (4 ml) were added thereto, and the mixture was refluxed for 3 hr. The reaction solution was partitioned between ethyl acetate and water, and the resulting organic layer was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography to give an oil. The oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals (656 mg, yield; 66%).

Hydrochloride:

m.p.; 140-144°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 1.45-1.49(m,2H), 1.63-1.70(m,2H), 2.51(br,2H), 2.65(t,J=7.2Hz,2H), 3.18-3.28(m,2H), 3.30-3.38(m,2H), 3.54(t,J=13.2Hz,2H), 3.62(d,J=10.8Hz,2H), 3.98(d,J=12.4Hz,2H), 7.33(d,J=8.4Hz,2H), 7.59(t,J=8.0Hz,1H), 7.74(t,J=8.0Hz,1H), 7.98(d,J=8.0Hz,1H), 8.05(s,1H), 8.11(d,J=8.4Hz,2H), 8.12(d,J=8.0Hz,1H).

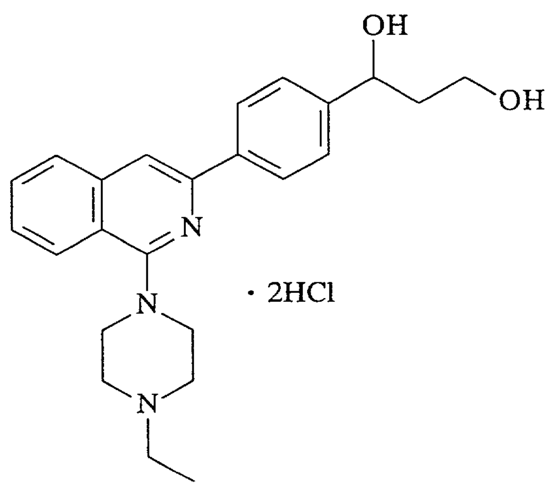
MS(FAB) m/z 390(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.61-1.77(m,4H), 2.56(q,J=7.2Hz,2H), 2.71(t,J=7.2Hz,2H), 2.76(br,4H), 3.59(br,4H), 3.68(t,J=6.4Hz,2H), 7.28(d,J=8.4Hz,2H), 7.45(dt,J=8.0,1.2Hz,1H),

7.58(dt,J=8.0,1.2Hz,1H), 7.67(s,1H), 7.78(d,J=8.0Hz,1H), 8.07(d,J=8.0Hz,1H), 8.09(d,J=8.4Hz,2H).

Example 24 Synthesis of 3-[4-(1,3-dihydroxypropyl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners as in Examples 161-2 and then 20, an oil was obtained from 1-bromo-4-(1,3-isopropylidenepropyl)benzene (2.21 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (700 mg). Tetrahydrofuran (15 ml) and 1N hydrochloric acid (2 ml) were added thereto, and the resulting mixture was reacted at room temperature for 3 hr. The reaction solution was basified with a 1N aqueous solution of sodium hydroxide and extracted with ethyl acetate. The resulting organic layer was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography, to give an oil. It was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals (387 mg, yield; 44%).

Hydrochloride:

m.p.; 145-147°C

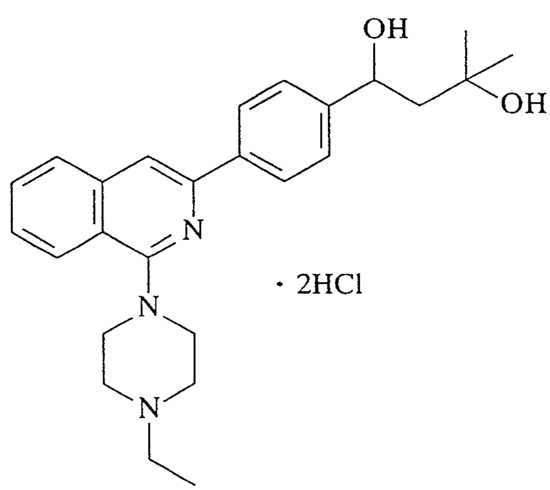
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 1.70-1.84(m,2H), 3.18-3.26(m,2H), 3.32-3.39(m,2H), 3.45-3.58(m,4H), 3.62(d,J=6.8Hz,2H), 4.00(d,J=13.2Hz,2H), 4.72-4.75(m,1H), 7.46(d,J=8.4Hz,2H), 7.61(dt,J=8.0,1.2Hz,1H), 7.74(dt,J=8.0,1.2Hz,1H), 7.99(d,J=8.0Hz,1H), 8.07(s,1H), 8.12(d,J=8.0Hz,1H), 8.15(d,J=8.4Hz,2H).

MS(FAB) m/z 392(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.07(t,J=7.2Hz,3H), 1.70-1.90(m,2H), 2.45(q,J=7.2Hz,2H), 2.67(br,4H), 3.35-3.60(m,2H), 3.44(br,4H), 4.61(t,J=4.8Hz,1H), 4.73-4.75(m,1H), 5.20(d,J=4.8Hz,1H), 7.44(d,J=8.4Hz,2H), 7.55(t,J=8.0Hz,1H), 7.69(t,J=8.0Hz,1H), 7.93(d,J=8.0Hz,1H), 7.95(s,1H), 8.05(d,J=8.0Hz,1H), 8.14(d,J=8.4Hz,2H).

<u>Example 25 Synthesis of 3-[4-(1,3-dihydroxy-3-methylbutyl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline</u>



In the same manners as in Examples 161-2 and then 20, an oil was obtained from 1-bromo-4-(1,3-isopropylidene-3-methyl-butyl)benzene (1.87 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (413 mg). Tetrahydrofuran (10 ml) and a 1N aqueous solution of hydrochloric acid (0.5 ml) were added thereto, and the mixture was reacted at room temperature for 3 hr. The reaction solution was basified with a 1N aqueous solution of sodium hydroxide and extracted with ethyl acetate. The resulting organic layer was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography, to give an oil. The oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals (289 mg, yield; 69%).

Hydrochloride:

m.p.; 190-192°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.19(s,3H), 1.26(s,3H), 1.33(t,J=7.2Hz,3H), 3.22-3.26(m,2H), 3.37(br,2H), 3.50(t,J=13.6Hz,2H), 3.63(d,J=7.2Hz,2H), 4.00(d,J=12.8Hz,2H), 4.59(br,2H), 4.94(d,J=7.2Hz,1H), 7.47(d,J=8.0Hz,2H), 7.60(t,J=8.0Hz,1H), 7.74(t,J=8.0Hz,1H), 7.90(d,J=8.0Hz,1H), 8.07-8.16(m,4H).

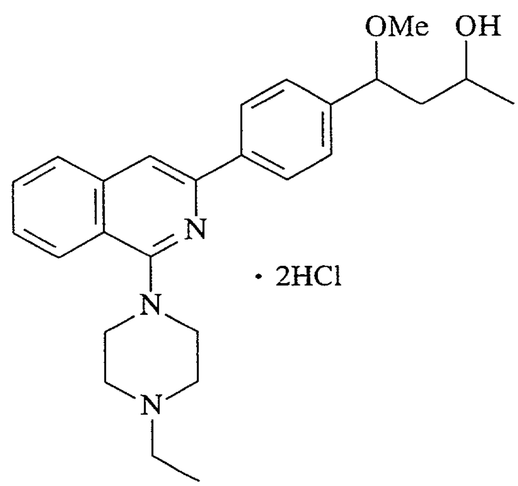
MS(FAB) m/z 420$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.08(t,J=7.2Hz,3H), 1.19(s,3H), 1.26(s,3H), 1.65-1.80(m,2H), 2.65(q,J=7.2Hz,2H), 2.67(br,4H),

3.44(br,4H), 4.74(s,1H), 4.91-4.93(m,1H), 5.41(d,J=3.2Hz,1H), 7.44(d,J=8.4Hz,2H), 7.55(d,J=8.0Hz,1H), 7.69(dt,J=8.0Hz,1H), 7.93(d,J=8.0Hz,1H), 7.95(s,1H), 8.05(d,J=8.0Hz,1H), 8.13(d,J=8.4Hz,2H).

Example 26 Synthesis of 3-[4-(3-hydroxy-1-methoxybutyl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline



In the same manners as in Examples 161-2 and then 20, an oil was obtained from 1-bromo-4-(3-hydroxy-1-methoxybutyl)benzene (1.59 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (957 mg). Methanol (10 ml) and a 1N aqueous solution of sodium hydroxide (1 ml) were added thereto, and then the resulting mixture was refluxed for 3 hr. The reaction solution was partitioned between ethyl acetate and water, and the resulting organic layer was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography, to give an oil. The oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals (196

mg, yield; 20%).

Hydrochloride:

m.p.; 171-174℃

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.06(t,J=6.4Hz,3H), 1.33(t,J=7.2Hz,3H), 1.52-1.60(m,1H), 1.91-1.98(m,1H), 3.12(s,3H), 3.21-3.26(m,2H), 3.34-3.39(m,2H), 3.39-3.51(m,4H), 3.63(d,J=12.0Hz,2H), 4.01(d,J=13.6Hz,2H), 4.35(t,J=6.4Hz,2H), 7.43(d,J=8.0Hz,2H), 7.62(t,J=8.0Hz,1H), 7.75(t,J=8.0Hz,1H), 7.99(d,J=8.0Hz,1H), 8.09(s,1H), 8.12(d,J=8.0Hz,1H), 8.18(d,J=8.0Hz,2H).

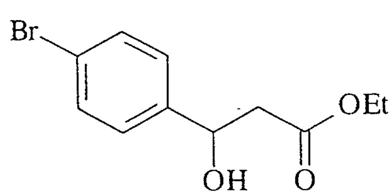
MS(FAB) m/z 420(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.71-1.76(m,1H), 1.92-2.00(m,1H), 2.56(q,J=7.2Hz,2H), 2.76(br,4H), 3.27(s,3H), 3.60(br,4H), 3.74(br,1H), 4.06-4.10(m,2H), 4.45(dd,J=10.0,3.2Hz,1H), 7.40(d,J=8.4Hz,2H), 7.47(ddd,J=8.4,8.0,1.2Hz,1H), 7.59(ddd,J=8.4,8.0,1.2Hz,1H), 7.70(s,1H), 7.80(d,J=8.0Hz,1H), 8.08(d,J=8.4Hz,1H), 8.17(dd,J=8.4Hz,2H).

Example 27 Synthesis of 1(1-ethylpiperazin-4-yl)-3-[4-(3-hydroxy-1-fluoropropyl)phenyl]isoquinoline

(27-1) Ethyl 3-(4-Bromophenyl)-3-hydroxypropionate

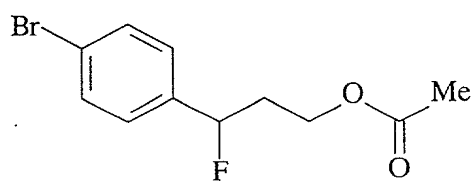


Ethyl acetate (5.8 ml) was dissolved in tetrahydrofuran

(80 ml), to which was then added 1.5M lithium diisoprypylamide/cyclohexane solution (43 ml) in nitrogen atmosphere at -70 °C, and then the mixture was stirred for 15 min. 4-Bromobenzaldehyde (10.151 g)/tetrahydrofuran (10 ml) solution was added to the reaction mixture, which was then stirred for 30 min. A saturated aqueous solution of ammonium chloride was added thereto, and then it was extracted with in ethyl acetate. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by (NH) silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a yellow oil (11.906 g, yield; 80%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.27(3H,t,J=7.2Hz), 2.68-2.71(2H,m), 3.38(1H,d,J=3.6Hz), 4.19(2H,q,J=7.2Hz), 5.07-5.12(1H,m), 7.26(2H,d,J=8.8Hz), 7.48(2H,d,J=8.8Hz).

(27-2) 3-(4-Bromophenyl)-3-fluoropropyl acetate

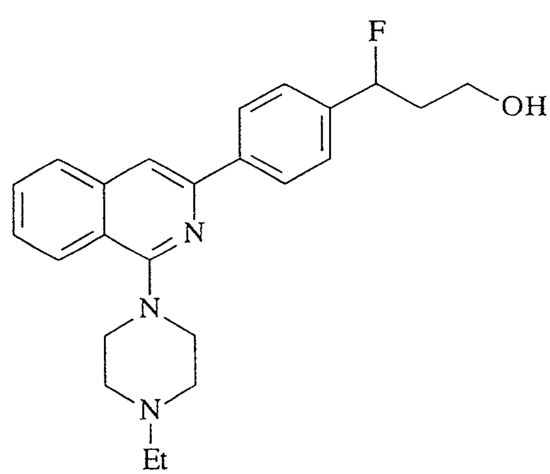


A product obtained from ethyl 3-(4-bromophenyl)-3-hydroxypropionate (7.433 g) and diethylaminosulfur trifluoride (237 ml) in the same treatment as in Example 132 was dissolved in tetrahydrofuran (60 ml). Lithium aluminium hydride (1.005 g) was added thereto under ice-cooling, and then the mixture was stirred for 20 min. To the reaction mixture were sequentially added water (1 ml), 5N sodium hydroxide (1

ml) and water (3 ml), the resulting insoluble matters were filtered off through Celite, and the resulting filtrate was evaporated. The resulting residue was dissolved in pyridine (30 ml), acetic anhydride (3.5 ml) and dimethylaminopyridine (182 mg) were added thereto, and then the mixture was stirred at room temperature for 30 min. The reaction solution was evaporated, and the resulting residue was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give 4.542 g of the title compound as a pale yellow oil (yield; 61%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 2.06(3H,s), 2.06-2.31(2H,m), 4.11-4.29(2H,m), 5.54(1H,ddd,J=47.6Hz,8.8Hz,4Hz), 7.22(2H,d,J=8.8Hz), 7.52(2H,d,J=8.8Hz).

<u>(27-3) 1-(1-Ethylpiperazin-4-yl)-3-[4-(3-hydroxy-1-fluoropropyl)phenyl]isoquinoline</u>



Acetate 3-(4-bromophenyl)-3-fluoropropane ester (833 mg)

and bis(tributyltin) (2 ml) were treated in the same manner as in Example 161-2, and then treated with 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (321 mg) in the same manner as in Example 300, to give the hydrochloride of the title compound as hygroscopic yellow crystals (187 mg, yield; 40%).

Hydrochloride:

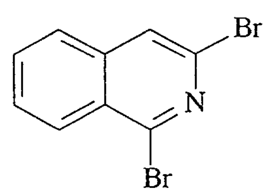
m.p.; 141-146°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.31(3H,t,J=7.2Hz), 1.70-2.20(2H,m), 3.21(1H,q,J=7.2Hz), 3.22(1H,q,J=7.2Hz), 3.32(1H,t,J=10.4Hz), 3.35(1H,t,J=10.4Hz), 3.43-3.53(4H,m), 3.61(2H,d,J=10.4Hz), 4.08(2H,d,J=13.2Hz), 5.70(1H,ddd,J=48Hz,9.2Hz,4Hz), 7.39-7.76(4H,m), 7.95-8.24(5H,m), 10.75-10.85(1H,br-s).

ESI-Mass ; 394(MH$^+$).

Example 28 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(4-hydroxymethyl-3-fluoro)phenyl]isoquinoline hydrochloride

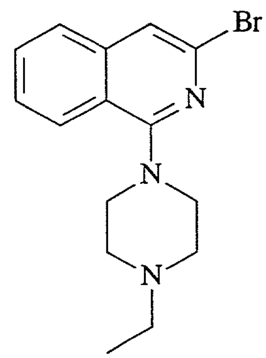
(28-1) 1,3-Dibromoisoquinoline



1,4-Dioxane (84 ml) was added to phosphorus oxybromide (23.5 g), and dissolved at room temperature. To the mixture was added homophthalimide (6.0 g) little by little, and then heated under reflux for 35 min. The reaction solution was cooled, dissolved in chloroform (300 ml) and methanol (50 ml), and evaporated. The resulting crystals were collected by

filtration, washed with 2-propanol, dried at 50°C for 1 hr, to give the title compound as pale brown crystals (6.1 g, yield; 57%).

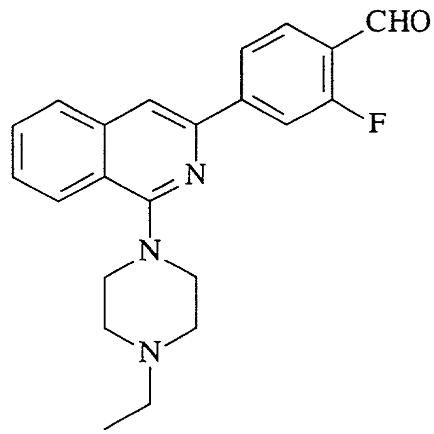
(28-2) 3-Bromo-1-(4-ethylpiperazin-1-yl)isoquinoline



1,3-Dibromoisoquinoline (2.70 g), N-ethylpiperazine (1.16 g) and potassium carbonate (3.50 g) were reacted in DMF (30 ml) at 80 °C for 5 hr. The reaction solution was evaporated, and then partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and evaporated. The resulting residue was purified by NH silica gel column chromatography (ethyl acetate/n-hexane system), to give the title compound (2.21 g) as a pale yellow oil.

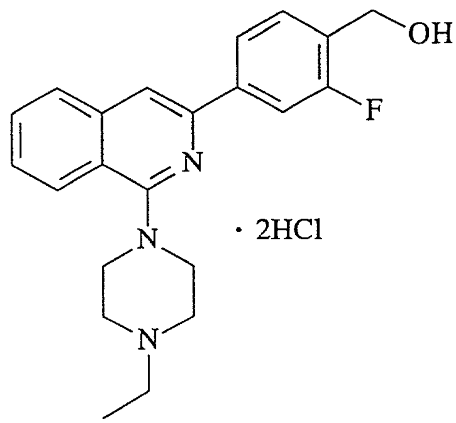
^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.54(q,J=7.2Hz,2H), 2.66-2.73(m,4H), 3.52-3.58(m,4H), 7.40(s,1H), 7.45(dt,J=8.0,2.0Hz,1H), 7.58(dt,J=8.0,2.0Hz,1H), 7.62(dd,J=8.0,2.0Hz,1H), 7.98(dd,J=8.0,2.0Hz,1H).

(28-3) 1-(4-Ethylpiperazin-1-yl)-3-[4-(3-fluoro-4-formyl)phenyl]isoquinoline



2-Fluoro-4-tributylstannylbenzaldehyde (2.20 g) produced by heating 4-bromo-2-fluorobenzaldehyde (5.0 g) and hexabutylditin (14.3 g) in xylene (50 ml) in the presence of tetrakistriphenylphosphine (0.38 g) was reacted with 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.20 g) obtained in (28-2) in the presence of tetrakistriphenylphosphine (0.3 g) in xylene in nitrogen atmosphere for 4 hr. After cooling, the reaction solution was extracted with a 2N aqueous solution of hydrochloric acid, basified with a 5N aqueous solution of sodium hydroxide, and then reverse-extracted with ethyl acetate. The resulting organic layer was washed with water and brine, dried and concentrated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.92 g of the title compound.

(28-4) 1-(4-Ethylpiperazin-1-yl)-3-[4-(4-hydroxymethyl-3-fluoro)phenyl]isoquinoline hydrochloride



Sodium borohydride (0.10 g) was added to a solution of 1-(4-ethylpiperazin-1-yl)-3-[4-(3-fluoro-4-formyl)phenyl]isoquinoline (0.25 g) in methanol (20 ml) at 0°C. After stirring the reaction solution for 30 min, it was concentrated. To the resulting residue was added water, which was then extracted with methylene chloride, dried and concentrated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the free compound of the title compound as a pale yellow oil. The oil was converted into a hydrochloride in a conventional manner, to give 0.15 g of the title compound as a yellow powder.

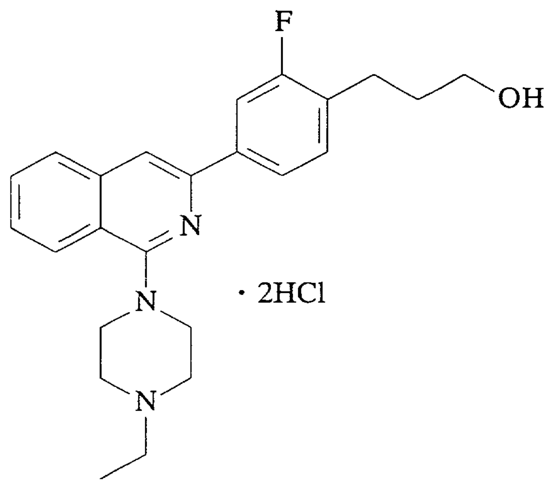
Hydrochloride:

m.p.; 228°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 3.19-3.28(m,2H), 3.35(br-q,2H), 3.49-3.67(m,4H), 4.01(br-d,2H), 4.62(s,2H), 7.57-7.67(m,1H), 7.76(br-t,1H), 7.94-8.01(m,2H), 8.05(dd,J=8.0,1.6Hz,1H), 8.13(d,J=8.4Hz,1H), 8.16(s,1H).

MS(FAB) m/z 366(M+H)$^+$.

<u>Example 29 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[3-fluoro-4-(1-hydroxypropyl)phenyl]isoquinoline hydrochloride</u>



Ethyl 2-fluoro-4-tributylstannylcinnamate (1.918 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.090 g) were reacted in the presence of tetrakistriphenylphosphine (0.153 g) in xylene (20 ml) in nitrogen atmosphere for 2 hr. After cooling, the reaction solution was filtered. The resulting filtrate was extracted with a 5N aqueous solution of hydrochloric acid. The resulting aqueous layer was basified with a 5N aqueous solution of sodium hydroxide, and then extracted with ethyl acetate. The resulting organic layer was washed with water and brine, dried and concentrated. The resulting 1-(4-ethylpiperazin-1-yl)-3-[3-fluoro-4-(2-ethoxycarbonylethen-1-yl)phenyl]isoquinoline (1.222 g) was dissolved in tetrahydrofuran (10 ml), which was then added dropwise into a suspension of lithium aluminium hydride (0.211 g). The reaction solution was heated under reflux for 8 hr, and then cooled. Then, water, an aqueous solution of sodium

hydroxide and water were added thereto in this order, and then stirred at room temperature for 1 hr. The resulting precipitates were filtered off, followed by washing with ethyl acetate. The filtrate was concentrated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.226 g of 1-(4-ethylpiperazin-1-yl)-3-[3-fluoro-4-(1-hydroxypropyl)phenyl]isoquinoline as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.90-1.97(m,2H), 2.56(q,J=7.2Hz,2H), 2.76(br-t,4H), 2.80(t,J=7.4Hz,2H), 3.59(br-t,4H), 3.72(t,J=7.4Hz,2H), 7.16-7.19(m,1H), 7.47(br-t,1H), 7.60(br-t,1H), 7.66(s,1H), 7.79(d,J=8.4Hz,1H), 7.85-7.89(m,2H), 8.08(d,J=8.0Hz,1H).

The free compound was converted into a hydrochloride in a conventional manner, to give the title compound as a yellow powder.

Hydrochloride:

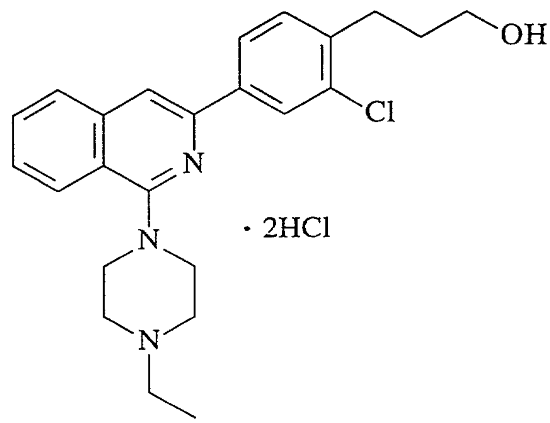
m.p.; 126-127°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.32(t,J=7.2Hz,3H), 1.71-1.78(m,2H), 2.70(br-t,2H), 3.21-3.28(m,2H), 3.31-3.40(m,2H), 3.46(t,J=6.4Hz,2H), 3.48(br-t,2H), 3.64(br-d,2H), 4.02(br-d,2H), 7.42(dd,J=8.2,8.2Hz,1H), 7.63(br-t,1H), 7.76(br-t,1H), 7.93-8.00(m,3H), 8.12-8.14(m,2H).

MS(FAB) m/z 394$(M+H)^+$.

<u>Example 30 Synthesis of 3-[3-chloro-4-(3-</u>

hydroxypropyl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners as in Examples 161-2 and then 20, an oil was obtained from 1-bromo-3-chloro-4-ethylpropionitebenzene (1.92 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.3 g). Under ice-cooling, tetrahydrofuran (20 ml) and lithium aluminium hydride (120 mg) were added to the oil, which was then reacted at room temperature for 1 hr. Thereafter, water (0.1 ml), a 5N aqueous solution of sodium hydroxide (0.1 ml) and water (0.3 ml) were added sequentially to the resulting reaction mixture, and the mixture was stirred at room temperature for 1 hr. The resulting residue was filtered, washed with ethyl acetate, and then purified by silica gel column chromatography, to give an oil. The oil was converted into a hydrochloride in a conventional manner, give the hydrochloride of the title compound as yellow crystals (900 mg, yield; 71%).

Hydrochloride:

m.p.; 123-124°C

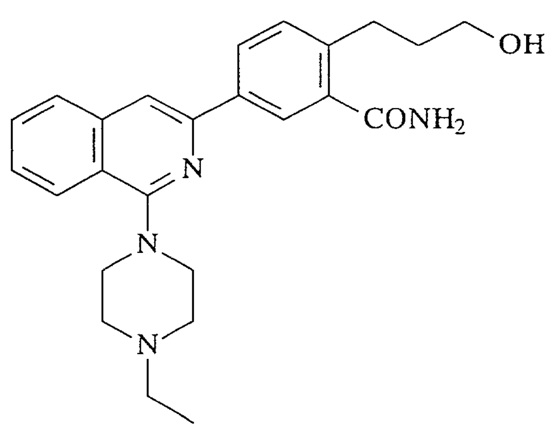
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 1.72-1.82(m,2H), 2.79(t,J=7.6Hz,2H), 3.20-3.28(m,2H), 3.32-3.40(m,2H), 3.48(t,J=6.4Hz,4H), 3.65(d,J=11.6Hz,2H), 4.00(d,J=13.2Hz,2H), 7.47(d,J=8.0Hz,1H), 7.63(t,J=8.0Hz,1H), 7.76(t,J=8.0Hz,1H), 7.99(d,J=8.0Hz,1H), 8.11(dd,J=8.0,1.6Hz,1H), 8.13(d,J=8.0Hz,1H), 8.16(s,1H), 8.22(d,J=1.6Hz,1H).

MS(FAB) m/z 410(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.67(t,J=7.2Hz,3H), 1.90-1.97(m,2H), 2.55(q,J=7.2Hz,2H), 2.76(br,4H), 2.88(t,J=7.6Hz,2H), 3.58(br,4H), 3.72(t,J=6.4Hz,2H), 7.32(d,J=8.0Hz,1H), 7.47(t,J=8.4Hz,1H), 7.59(t,J=8.4Hz,1H), 7.65(s,1H), 7.78(d,J=8.4Hz,1H), 7.96(dd,J=8.0,2.0Hz,1H), 8.07(d,J=8.4Hz,1H), 8.16(d,J=2.0Hz,1H).

<u>Example 31 Synthesis of 3-[3-carboxamide-4-(3-hydroxypropyl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline</u>



In the same manners as in Examples 161-2 and then 20, an yellow oil was obtained from 1-bromo-3-carboxamide-4-(3-

acetoxypropyl)benzene (1.04 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (409 mg). Methanol (10 ml) and a 1N aqueous solution of sodium hydroxide solution (1 ml) were added to the oil, which was then reacted at room temperature overnight. The reaction solution was partitioned between ethyl acetate and water, and the resulting organic layer was washed with brine, dried and evaporated. Then, it was recrystallized from methanol/diethyl ether, to give the title compound as white crystals (125 mg, yield; 30%).

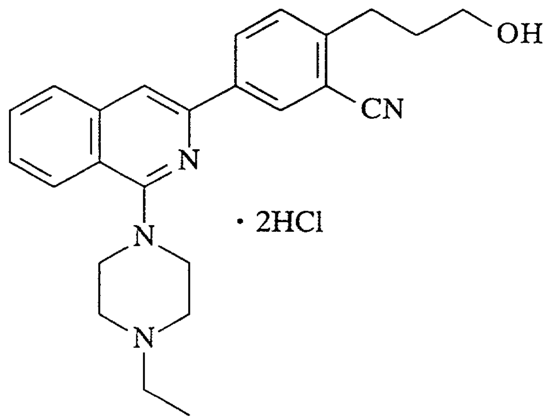
Free compound:

m.p.; 213-218°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.08(t,J=7.2Hz,3H), 1.76(tt,J=8.0,7.6Hz,2H), 2.45(q,J=7.2Hz,2H), 2.68(br,4H), 2.80(t,J=8.0Hz,2H), 3.44(br,4H), 3.39-3.44(m,2H), 4.54(t,J=5.2Hz,1H), 7.37(d,J=8.0Hz,1H), 7.45(s,1H), 7.57(t,J=8.4Hz,1H), 7.70(t,J=8.4Hz,1H), 7.90(s,1H), 7.94(d,J=8.4Hz,1H), 7.99(s,1H), 8.06(d,J=8.4Hz,1H), 8.13(s,1H), 8.14(dd,J=8.0,2.0Hz,1H).

MS(FAB) m/z 419(M+H)$^+$.

Example 32 Synthesis of 3-[3-cyano-4-(3-hydroxypropyl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners as in Examples 161-2 and then 20, a yellow oil was obtained from 5-bromo-3-carboxamide-4-(3-acetoxypropyl)benzene (1.15 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (442 mg). THF (5 ml), carbon tetrachloride (5 ml) and triphenylphosphine (588 mg) were added to the oil, and then it was reacted at 60°C for 4 hr. The reaction solution was partitioned between ethyl acetate and water, and the resulting product was extracted with 2N hydrochloric acid. The resulting aqueous layer was basified with 2N sodium hydroxide, and then reverse-extracted with ethyl acetate. The resulting organic layer was washed with water, dried and evaporated. To the resulting residue were added methanol (10 ml) and a 1N aqueous solution of sodium hydroxide (1 ml), and the mixture was reacted at 50°C for 30 min. The reaction solution was partitioned between ethyl acetate and water. The resulting organic layer was washed with brine, dried and evaporated. Thereafter, it was purified by NH-silica gel column chromatography (ethyl acetate/hexane system), to give a yellow oil (191 mg, yield; 45%). The oil was converted into

a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as white crystals.

Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.35(t,J=7.2Hz,3H), 1.78-1.85(m,2H), 2.89(t,J=8.0Hz,2H), 3.20-3.25(m,2H), 3.33-3.40(m,2H), 3.49(t,J=6.4Hz,2H), 3.55-3.65(m,4H), 4.02(d,J=13.6Hz,2H), 7.61(d,J=8.4Hz,1H), 7.65(t,J=8.4Hz,1H), 7.78(t,J=8.4Hz,1H), 7.99(d,J=8.4Hz,1H), 8.14(d,J=8.4Hz,1H), 8.22(s,1H), 8.45(dd,J=8.4,2.0Hz,1H), 8.54(d,J=2.0Hz,1H).

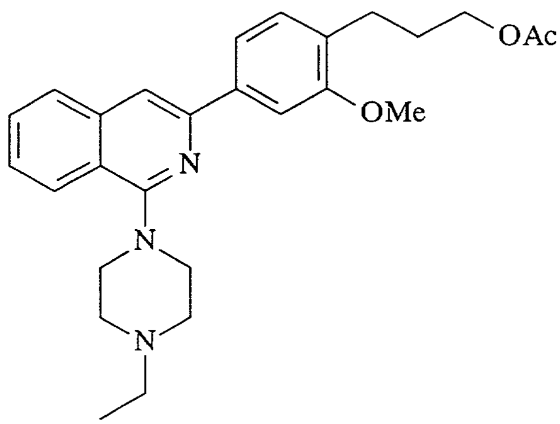
MS(FAB) m/z 401$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.20(t,J=7.2Hz,3H), 1.96-2.05(m,2H), 2.59(q,J=7.2Hz,2H), 2.79(br,4H), 3.01(t,J=7.2Hz,2H), 3.61(br,4H), 3.75(t,J=6.4Hz,2H), 7.44(d,J=8.0Hz,1H), 7.51(ddd,J=8.4,8.0,1.2Hz,1H), 7.62(ddd,J=8.4,8.0,1.2Hz,1H), 7.68(s,1H), 7.81(d,J=8.0Hz,1H), 8.08(d,J=8.4Hz,1H), 8.29(dd,J=8.0,1.6Hz,1H), 8.43(d,J=1.6Hz,1H).

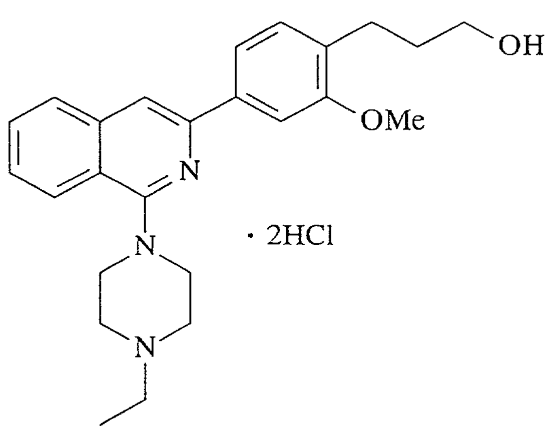
Example 33 Synthesis of 1-(4-ethylpiperazin-1-yl]-3-[4-(3-hydroxypropyl)-3-methoxyphenyl]isoquinoline hydrochloride

(33-1) 1-(4-Ethylpiperazin-1-yl)-3-[4-(3-acetoxypropyl)-3-methoxyphenyl]isoquinoline



2-(3-Acetoxypropyl)-5-tributylstannylanisole (0.92 g) and 3-bromo-1-((4-ethylpiperazin-1-yl)isoquinoline (0.37 g) were reacted in the presence of tetrakistriphenylphosphine (0.3 g) in xylene in nitrogen atmosphere for 4 hr. After cooling, the reaction solution was filtered and extracted with ethyl acetate. The resulting organic layer was washed with water and brine, dried and concentrated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.28 g of the title compound.

(33-2) 1-(4-Ethylpiperazin-1-yl)-3-[4-(3-hydroxypropyl)-3-methoxyphenyl]isoquinoline hydrochloride



1-(4-Ethylpiperazin-1-yl)-3-[4-(3-acetoxypropyl)-3-

methoxyphenyl]isoquinoline was dissolved in methanol (10 ml), a 2N aqueous solution of sodium hydroxide (2 ml) was added thereto, ahd then the mixture was reacted at 50°C for 2 hr. The reaction solution was concentrated and extracted with ethyl acetate. The resulting organic layer was washed with water and brine, dried and concentrated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), which was then converted into a hydrochloride in a conventional manner to give 0.18 g of the title compound as a yellow powder.

Hydrochloride:

m.p.; 123-124℃

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.32(t,J=7.2Hz,3H), 1.66-1.76(m,2H), 2.59-2.68(m,2H), 3.20-3.29(m,2H), 3.36(br-q,2H), 3.41-3.55(m,4H), 3.64(br-d,2H), 3.93(s,3H), 4.02(br-d,2H), 7.26(d,J=8.4Hz,1H), 7.61(br-t,1H), 7.76(br-t,1H), 7.70-7.78(m,2H), 7.99(d,J=8.4Hz,1H), 8.09-8.14(m,2H).

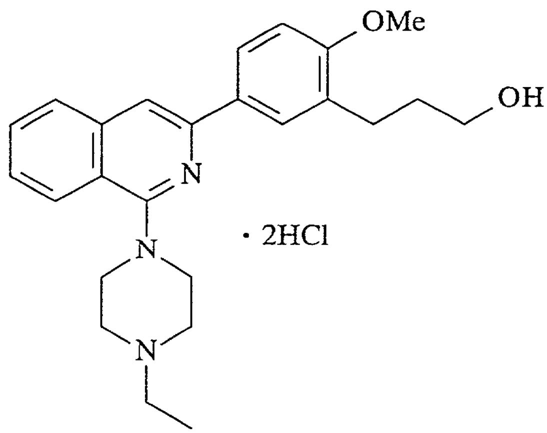
MS(FAB) m/z 406(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 1.84-1.92(m,2H), 2.54(q,J=7.2Hz,3H), 2.73-2.81(m,6H), 3.58(m,4H), 3.63(t,J=7.6Hz,3H), 3.96(s,3H), 7.23(d,J=6.4Hz,1H), 7.45(t,J=7.6Hz,1H), 7.57(t,J=7.6Hz,1H), 7.65(br-d,1H), 7.68(s,1H), 7.77-7.82(m,2H), 8.07(d,J=8.0Hz,1H).

Example 34 Synthesis of 3-[3-(3-hydroxypropyl)-4-methoxyphenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline

hydrochloride



In the same manners as in Examples 161-2, and then 20, an oil was obtained from 1-bromo-3-(3-acetoxypropyl)-4-methoxybenzene (2.57 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.7 g). Methanol (10 ml) and a 1N aqueous solution of sodium hydroxide (2ml) were added to the resulting oil, which was then heated under reflux for 3 hr. After cooling the reaction mixture, it was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography, to give an oil. Then, the oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals (1.2 g, yield; 74%).

Hydrochloride:

m.p.; 157-160℃

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 1.72-1.79(m,2H), 2.67(t,J=7.2Hz,2H), 3.18-3.26(m,2H), 3.32-3.39(m,2H), 3.47(t,J=6.4Hz,2H), 3.53(t,J=12.8Hz,2H),

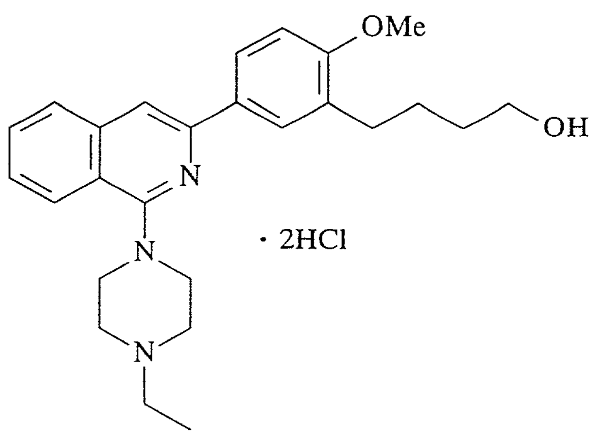
3.64(d,J=11.2Hz,2H), 3.86(s,3H), 3.99(d,J=13.2Hz,2H), 7.08(d,J=8.4Hz,1H), 7.57(t,J=8.0Hz,1H), 7.72(t,J=8.0Hz,1H), 7.95(d,J=8.0Hz,1H), 7.96(d,J=2.4Hz,1H), 7.99(s,1H), 8.04(dd,J=8.4,2.4Hz,1H), 8.09(d,J=8.0Hz,1H).

MS(FAB) m/z 406$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.93(tt,J=7.2,6.4Hz,2H), 2.56(q,J=7.2Hz,2H), 2.77(br,4H), 2.82(t,J=7.2Hz,2H), 3.58(br,4H), 3.66(t,J=6.4Hz,2H), 3.90(s,3H), 6.96(d,J=8.4Hz,1H), 7.43(ddd,J=8.4,8.0,1.2Hz,1H), 7.57(ddd,J=8.4,8.0,1.2Hz,1H), 7.62(s,1H), 7.77(d,J=8.0Hz,1H), 7.96(d,J=2.4Hz,1H), 8.03(dd,J=8.4,2.4Hz,1H), 8.06(d,J=8.4Hz,1H).

Example 35 Synthesis of 3-[3-(4-hydroxybutyl)-4-methoxyphenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners as in Examples 161-2, and then 20, an oil was obtained from 1-bromo-3-(4-acetoxybutyl)-4-methoxybenzene (1.54 g) and 3-bromo-1-(4-ethylpiperazin-1-

yl)isoquinoline (913 mg). Methanol (10 ml) and a 1N aqueous solution of sodium hydroxide (2 ml) were added to the oil, and then reacted at at room temperature for 2 hr. Then, the reaction solution was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography, to give an oil (805 mg, yield; 90%). The oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 128-132°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.31(t,J=7.2Hz,3H), 1.42-1.52(m,2H), 1.56-1.64(m,2H), 2.63(t,J=7.2Hz,2H), 3.16-3.24(m,2H), 3.28-3.38(m,2H), 3.41(t,J=6.4Hz,2H), 3.52(t,J=8.0Hz,2H), 3.62(d,J=11.2Hz,1H), 3.83(s,3H), 3.97(d,J=14.0Hz,1H), 7.06(d,J=8.8Hz,1H), 7.75(t,J=8.0Hz,1H), 7.70(t,J=8.0Hz,1H), 7.94(d,J=8.0Hz,1H), 7.94(d,J=2.4Hz,1H), 7.97(s,1H), 8.02(dd,J=8.8,2.4Hz,1H), 8.07(d,J=8.0Hz,1H).

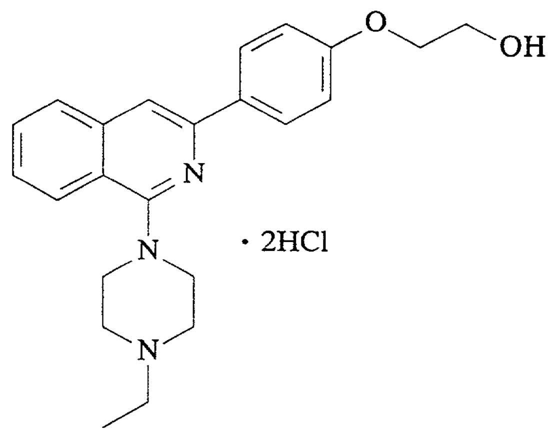
MS(FAB) m/z 420$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.67-1.74(m,4H), 2.56(q,J=7.2Hz,2H), 2.72-2.77(m,2H), 2.76(br,4H), 3.58(br,4H), 3.68-3.71(m,2H), 3.87(s,3H), 6.93(d,J=8.4Hz,1H), 7.42(ddd,J=8.4,8.0,1.2Hz,1H), 7.56(ddd,J=8.4,8.0,1.2Hz,1H), 7.61(s,1H), 7.76(d,J=8.0Hz,1H), 7.93(d,J=2.0Hz,1H),

8.00(dd,J=8.4,2.0Hz,1H), 8.05(d,J=8.4Hz,1H).

Example 36 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxyethoxy)phenyl]isoquinoline dihydrochloride



1-(4-Ethylpiperazin-1-yl)-3-(4-hydroxyphenyl)isoquinoline (1.0 g) obtained in Example 7 was dissolved in tetrahydrofuran (30 ml), followed by the addition of 60% sodium hydride (0.14 g). After the evolution of hydrogen ceased, 2-(t-butyl)dimethylsilyloxyethyl bromide (1.0 g) was added thereto, and the mixture was heated under reflux for 8 hr. The reaction solution was cooled to room temperature, and then it was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and evaporated. To the resulting residue was added a 2N aqueous solution of hydrochloric acid, which was then stirred at 50°C for 30 min. The reaction solution was washed with ethyl acetate. The resulting aqueous layer was basified by adding 2N sodium hydroxide thereto, and extracted with ethyl acetate. The resulting organic layer was washed with water, dried and evaporated. The resulting residue was purified by silica gel

column chromatography (methylene chloride/methanol system), to give the free compound of the title compound as a white powder. Then, the powder was converted into a hydrochloride in a conventional manner, to give 0.71 g of the title compound as a pale yellow powder.

Hydrochloride:

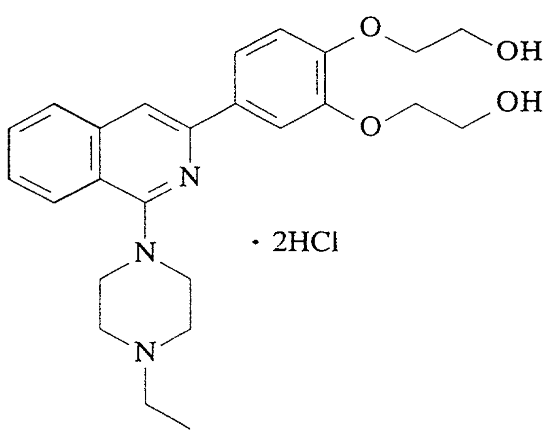
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 3.18-3.28(m,2H), 3.40(q,J=7.2Hz,2H), 3.50(br-t,2H), 3.62(br-d,2H), 3.97(br-d,2H), 6.90(d,J=8.8Hz,2H), 7.55(t,J=8.0Hz,1H), 7.71(t,J=8.0Hz,1H), 7.93(s,2H), 7.91-7.96(m,1H), 8.04(d,J=8.8Hz,2H), 8.08(d,J=8.8Hz,2H), 10.92(br-s,1H).

Free compound:

m.p.; 127-129°C

MS(FAB) m/z 378(M+H)$^+$.

Example 37 Synthesis of 3-[3,4-di(2-hydroxyethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



3-[3,4-Di(2-benzyloxyethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline (2.23 g) was obtained from 3-[3,4-di(2-benzyloxyethoxy)phenyl]-1-chloroisoquinoline

(1.97 g) obtained by the same treatment as in Example 20, potassium carbonate (2.5 g) and N-ethylpiperazine (5 ml). The resulting compound was converted into a hydrochloride, methanol (100 ml) and a palladium/carbon catalyst(50 mg) were added thereto, and then the mixture was reacted in hydrogen atmosphere at room temperature overnight. Subsequently, the reaction solution was filtered through Celite and evaporated. The resulting residue was basified by adding a 1N aqueous solution of sodium hydroxide thereto, and then it was extracted with ethyl acetate. The resulting organic layer was washed with brine, dried and evaporated. Then, the resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give a yellow oil (686 mg, yield; 44%). The oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as white crystals.

Hydrochloride:

m.p.; 130-132°C

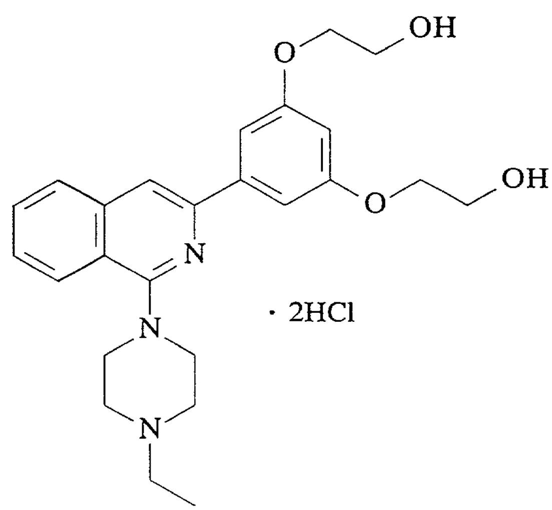
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 3.20-3.28(m,2H), 3.32-3.40(m,2H), 3.51(t,J=12.8Hz,2H), 3.63(d,J=11.2Hz,2H), 3.74-3.78(m,4H), 4.00(d,J=13.2Hz,2H), 4.07(t,J=5.2Hz,2H), 4.14(t,J=5.2Hz,2H), 7.11(d,J=8.4Hz,1H), 7.58(dt,J=8.0,1.2Hz,1H), 7.73(dt,J=8.0,1.2Hz,1H), 7.76(dd,J=8.4,2.4Hz,1H), 7.81(d,J=2.4Hz,1H), 7.96(d,J=8.0Hz,1H), 8.04(s,1H), 8.09(d,J=8.0Hz,1H).

MS(FAB) m/z 438(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.19(t,J=7.2Hz,3H), 2.57(q,J=7.2Hz,2H), 2.78(br,4H), 3.58(br,4H), 3.97-4.01(m,4H), 4.18-4.20(m,2H), 4.26-4.27(m,2H), 7.06(d,J=8.4Hz,1H), 7.47(ddd,J=8.4,8.0,1.2Hz,1H), 7.59(ddd,J=8.4,8.0,1.2Hz,1H), 7.63(s,1H), 7.78(dd,J=8.4,2.0Hz,1H), 7.79(d,J=8.0Hz,1H), 7.91(d,J=2.0Hz,1H), 8.08(d,J=8.4Hz,1H).

Example 38 Synthesis of 3-[3,5-di(2-hydroxyethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



From 3-[3,5-di(2-benzyloxyethoxy)phenyl]-1-chloroisoquinoline (1.24 g) obtained by the same treatment as in Example 20, potassium carbonate (1.6 g) and N-ethylpiperazine (5 ml), 3-(3,3-dibenzyloxyethoxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline (1.70 g) was obtained. The resulting compound was then converted into a hydrochloride, followed by the treatment with a palladium/carbon catalyst (50 mg) added, in the same manner as in Example 18, to give the free

compound of the title compound (510 mg, yield; 42%). The resulting free compound was then converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 232-234°C

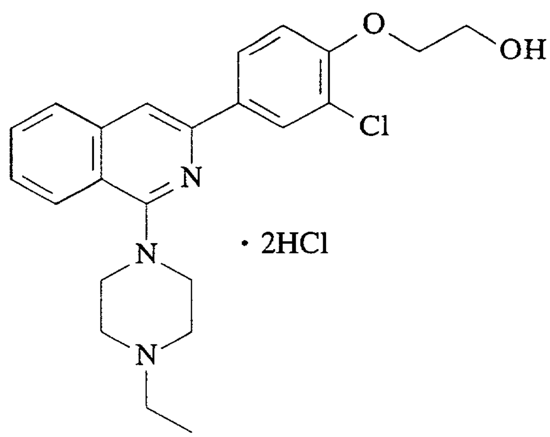
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 3.20-3.28(m,2H), 3.32-3.40(m,2H), 3.46-3.52(m,2H), 3.65(d,J=11.6Hz,2H), 3.76(t,J=5.2Hz,4H), 3.99(d,J=13.2Hz,2H), 4.09(t,J=5.2Hz,4H), 6.57(t,J=2.0Hz,1H), 7.37(s,1H), 7.38(s,1H), 7.62(t,J=8.0Hz,1H), 7.76(t,J=8.0Hz,1H), 7.99(d,J=8.0Hz,1H), 8.13(d,J=8.0Hz,1H), 8.15(s,1H).

MS(FAB) m/z 438$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.57(q,J=7.2Hz,2H), 2.78(br,4H), 3.58(br,4H), 4.01(t,J=4.8Hz,4H), 4.18(t,J=4.8Hz,4H), 6.54(t,J=2.0Hz,1H), 7.40(d,J=2.0Hz,2H), 7.48(ddd,J=8.4,8.0,1.2Hz,1H), 7.60(ddd,J=8.4,8.0,1.2Hz,1H), 7.67(s,1H), 7.79(d,J=8.0Hz,1H), 8.09(d,J=8.4Hz,1H).

Example 39 Synthesis of 3-[3-chloro-4-(2-hydroxyethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners as in Examples 161-2 and then 20, an oil was obtained from 1-bromo-3-chloro-4-(2-benzyloxyethoxy)benzene (2.52 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.3 g). Methanol (30 ml) and palladium/carbon catalyst (200 mg) were added to the oil, which was then reacted in hydrogen atmosphere at room temperature overnight. Thereafter, the reaction solution was filtered through Celite, and then evaporated. The resulting residue was basified by adding a 1N aqueous solution of sodium hydroxide thereto, which was then partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system), to give an oil (1.26 g, yield; 99 %). The oil was then converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 138-140°C

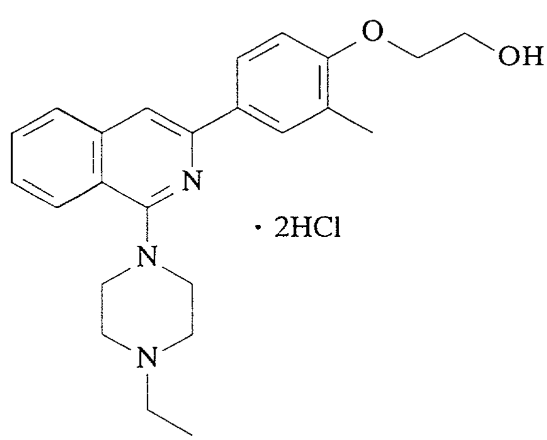
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 3.20-3.26(m,2H), 3.30-3.38(m,2H), 3.53(t,J=13.6Hz,2H), 3.64(d,J=11.6Hz,2H), 3.79(t,J=4.8Hz,2H), 3.99(d,J=13.6Hz,2H), 4.17(t,J=4.8Hz,2H), 7.30(d,J=8.8Hz,1H), 7.60(t,J=8.0Hz,1H), 7.74(t,J=8.0Hz,1H), 7.97(d,J=8.0Hz,1H), 8.09(s,1H), 8.11(d,J=8.0Hz,1H), 8.14(dd,J=8.4,2.4Hz,1H), 8.25(d,J=2.4Hz,1H).

MS(FAB) m/z 412(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.20(t,J=7.2Hz,3H), 2.59(q,J=7.2Hz,2H), 2.79(br,4H), 3.61(br,4H), 4.03(t,J=4.4Hz,2H), 4.22(t,J=4.4Hz,2H), 7.04(d,J=8.8Hz,1H), 7.46(ddd,J=8.4,8.0,1.2Hz,1H), 7.59(ddd,J=8.4,8.0,1.2Hz,1H), 7.61(s,1H), 7.77(d,J=8.0Hz,1H), 8.03(dd,J=8.4,2.4Hz,1H), 8.06(d,J=8.4Hz,1H), 8.19(d,J=2.4Hz,1H).

Example 40 Synthesis of 3-[3-methyl-4-(2-hydroxyethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners as in Examples 161-2 and then 20, an

oil was obtained from 1-bromo-3-methyl-4-(2-benzyloxyethoxy)benzene (1.48 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (495 mg). Methanol (30 ml) and palladium/carbon catalyst (100 mg) were added thereto, and the resulting mixture was reacted in hydrogen atmosphere at room temperature overnight. Thereafter, the reaction solution was filtered through Celite, and then evaporated. The resulting residue was basified by adding a 1N aqueous solution of sodium hydroxide thereto, and then partitioned between ethyl acetate and water. The resulting organic phase was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system), to give an oil (200 mg, yield; 44%). The oil was then converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 133-136°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 2.28(s,3H), 3.18-3.28(m,2H), 3.30-3.40(m,2H), 3.50(t,J=12.0Hz,2H), 3.64(d,J=10.8Hz,2H), 3.77(t,J=4.8Hz,2H), 3.99(d,J=14.0Hz,2H), 4.07(t,J=5.2Hz,2H), 7.06(d,J=8.8Hz,1H), 7.57(t,J=8.0Hz,1H), 7.72(t,J=8.0Hz,1H), 7.95(d,J=8.0Hz,1H), 7.99-8.03(m,3H), 8.09(d,J=8.0Hz,1H).

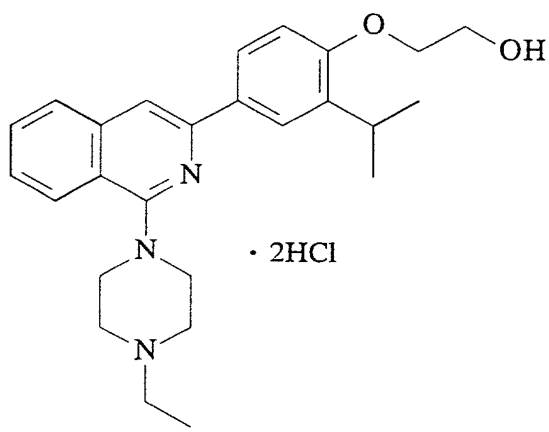
MS(FAB) m/z 392$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.20(t,J=7.2Hz,3H), 2.35(s,3H),

2.58(br,2H), 2.78(br,4H), 3.61(br,4H), 4.02(t,J=4.4Hz,2H), 4.17(t,J=4.4Hz,2H), 6.93(d,J=8.4Hz,1H), 7.33(t,J=8.4Hz,1H), 7.57(t,J=8.4Hz,1H), 7.62(s,1H), 7.77(d,J=8.4Hz,1H), 7.96(br,1H), 7.99(dd,J=8.4,2.0Hz,1H), 8.06(d,J=8.4Hz,1H).

Example 41 Synthesis of 3-[3-isopropyl-4-(2-hydroxyethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners as in Examples 161-2 and then 20, an oil was obtained from 1-bromo-3-isopropyl-4-(2-benzyloxyethoxy)benzene (3.45 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.0 g). Methanol (80 ml) and palladium/carbon catalyst (300 mg) were added thereto, which was then reacted in hydrogen atmosphere at room temperature overnight. After the reaction solution was filtered through Celite, it was evaporate. The resulting residue was basified by adding a 1N aqueous solution of sodium hydroxide thereto, which was then partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and concentrated. The resulting residue was

purified by silica gel column chromatography (hexane/ethyl acetate system), to give an oil (650 mg, yield; 40%). The oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 248-250°C (decomp.)

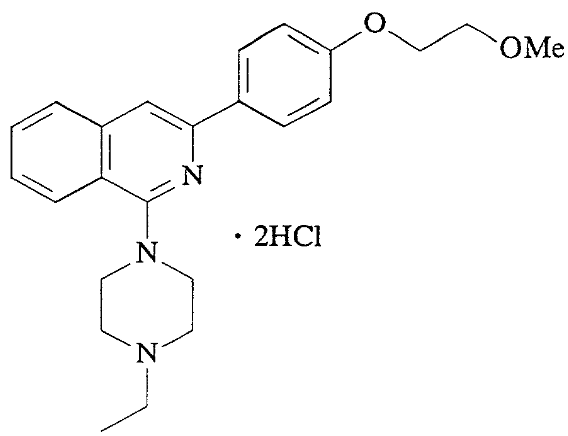
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.26(s,3H), 1.28(s,3H). 1.34(t,J=7.2Hz,3H), 3.26-3.28(m,2H), 3.30-3.39(m,3H), 3.60(t,J=8.8Hz,2H), 3.64(d,J=11.2Hz,2H), 3.78(t,J=4.8Hz,1H), 3.99(d,J=13.2Hz,2H), 4.08(t,J=4.8Hz,1H), 4.26-4.28(m,1H), 4.40-4.42(m,1H), 7.08(t,J=8.0Hz,1H), 7.57(t,J=8.0Hz,1H), 7.73(t,J=8.0Hz,1H), 7.98(d,J=8.0Hz,1H), 7.99-8.06(m,2H), 8.00(s,1H), 8.10(d,J=8.0Hz,1H).

MS(FAB) m/z 420(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.28(d,J=7.2Hz,6H), 2.56(q,J=7.2Hz,2H), 2.77(br,4H), 3.37-3.44(m,1H), 3.59(br,4H), 4.02(t,J=4.4Hz,2H), 4.16(t,J=4.4Hz,2H), 6.94(d,J=8.4Hz,1H), 7.43(ddd,J=8.4,8.0,1.2Hz,1H), 7.57(ddd,J=8.4,8.0,1.2Hz,1H), 7.62(s,1H), 7.78(d,J=8.0Hz,1H), 7.97(dd,J=8.4,2.4Hz,1H), 8.06(d,J=8.4Hz,1H), 8.07(d,J=2.4Hz,1H).

Example 42 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(2-methoxyethoxy)phenyl]isoquinoline dihydrochloride



1-(4-Ethylpiperazin-1-yl)-3-(4-hydroxyphenyl)isoquinoline (0.420 g) obtained in Example 7 was dissolved in N,N-dimethylformamide (5 ml), followed by the addition of 60% sodium hydride (0.06 g). After the evolution of hydrogen was ceased, 2-methoxyethyl bromide (178 μl) was added thereto, and the mixture was stirred 50°C for 3.5 hr. After the reaction solution was cooled to room temperature, it was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 1-(4-ethylpiperazin-1-yl)-3-[4-(2-methoxyethoxy)phenyl]isoquinoline as a white powder. The compound was converted into a hydrochloride in a conventional manner, to give 0.457 g of the title compound as a yellow powder.

Hydrochloride:

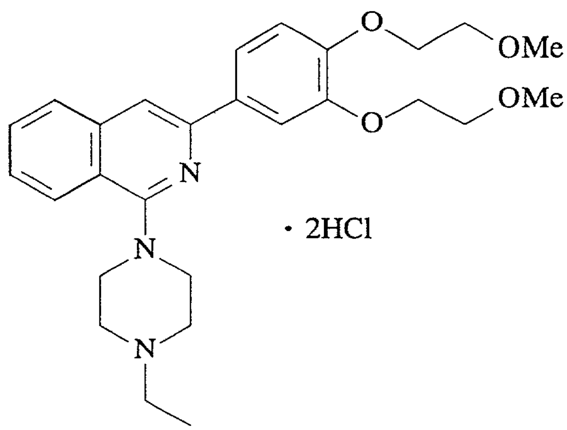
m.p.; 184.5-185°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_3); δ (ppm) 1.33(t,J=7.2Hz,3H), 3.21-3.27(m,2H), 3.31-3.39(2H,m), 3.33(s,3H), 3.49(br-t,2H),

3.63(br-d,2H), 3.69-3.71(m,2H), 3.99(br-d,2H), 4.16-4.18(m,2H), 7.08(d,J=8.8Hz,2H), 7.56(br-t,1H), 7.72(br-t,1H), 7.96(d,J=8.0Hz,1H), 8.00(s,1H), 8.10(d,J=8.4Hz,1H), 8.15(d,J=7.0Hz,2H), 10.74(br-s,1H).

MS(FAB) m/z 392(M+H)$^+$.

Example 43 Synthesis of 3-[3,4-di(2-methoxyethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manner as in Example 20, the free compound of the title compound was obtained (1.45 mg, yield; 95%) from 3-[3,4-di(methoxyethoxy)phenyl]-1-chloroisoquinoline (1.28 g), potassium carbonate (913 mg) and ethylpiperazine (30 ml). The compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 143-144°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 3.20-3.26(m,2H), 3.30-3.40(m,2H), 3.34(s,3H), 3.36(s,3H), 3.54-3.63(m,4H), 3.69-3.71(m,4H), 3.99(d,J=13.6Hz,2H), 4.16-

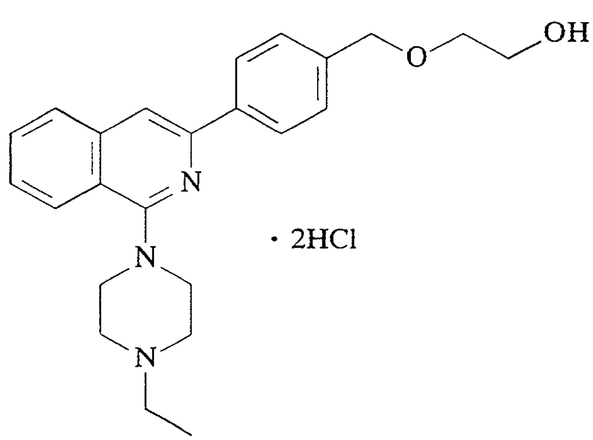
4.18(m,2H), 4.23-4.25(m,2H), 7.11(d,J=8.4Hz,1H), 7.58(dt,J=8.0,1.2Hz,1H), 7.73(td,J=8.0,1.2Hz,1H), 7.78(dd,J=8.4,2.0Hz,1H), 7.80(d,J=2.0Hz,1H), 7.96(d,J=8.0Hz,1H), 8.04(s,1H), 8.10(d,J=8.0Hz,1H).

MS(FAB) m/z 466$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.75(br,4H), 3.47(s,3H), 3.55(s,3H), 3.57(br,4H), 3.79-3.84(m,4H), 4.21-4.24(m,2H), 4.28-4.30(m,2H), 7.01(d,J=8.4Hz,1H), 7.43(dt,J=8.0,1.2Hz,1H), 7.56(dt,J=8.0,1.2Hz,1H), 7.61(s,1H), 7.72(dd,J=8.4,2.0Hz,1H), 7.76(d,J=8.0Hz,1H), 7.85(d,J=2.0Hz,1H), 8.06(d,J=8.0Hz,1H).

Example 44 Synthesis of 3-[4-(2-hydroxyethoxy)methylphenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners as in Examples 161-2 and then 20, an oil was obtained from 1-bromo-4-(2-benzyloxyethoxy)methylbenzene (1.72 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (854 mg). Methanol (20 ml)

and palladium/carbon catalyst (20 mg) were added thereto, which was then reacted in hydrogen atmosphere at room temperature overnight. Thereafter, the reaction solution was filtered through Celite, and then evaporated. The resulting residue was basified by adding a 1N aqueous solution of sodium hydroxide, which was then extracted with ethyl acetate. The resulting organic layer was washed with brine, dried and evaporated. Then, the resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give a yellow oil (567 mg, yield; 73%). The oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 129-131°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 3.20-3.28(m,2H), 3.33-3.39(m,2H), 3.55-3.64(m,8H), 4.00(d,J=13.6Hz,2H), 4.57(s,2H), 7.48(d,J=8.4Hz,2H), 7.61(t,J=8.0Hz,1H), 7.75(t,J=8.0Hz,1H), 7.99(d,J=8.0Hz,1H), 8.10(s,1H), 8.12(d,J=8.0Hz,1H), 8.19(d,J=8.4Hz,2H).

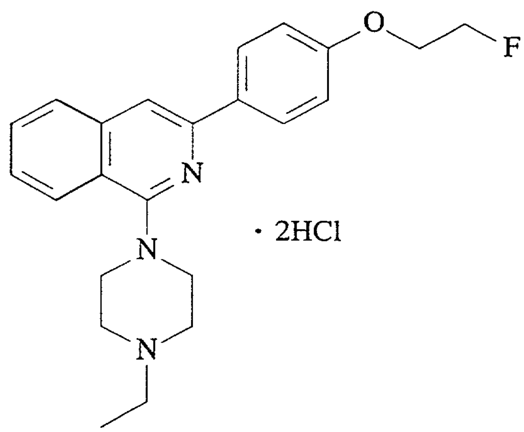
MS(FAB) m/z 392(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.77(br,4H), 3.60(br,4H), 3.64(t,J=4.8Hz,2H), 3.79(t,J=4.4Hz,2H), 4.63(s,2H), 7.44(d,J=8.4Hz,2H), 7.47(dt,J=8.4,1.2Hz,1H), 7.59(dt,J=8.4,1.2Hz,1H), 7.69(s,1H), 7.79(d,J=8.4Hz,1H),

8.08(d,J=8.4Hz,1H), 8.16(d,J=8.4Hz,2H).

Example 45 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(2-fluoroethoxy)phenyl]isoquinoline dihydrochloride



1-(4-Ethylpiperazin-1-yl)-3-(4-hydroxyphenyl)isoquinoline (0.514 g) obtained in Example 7 was dissolved in N, N-dimethylformamide (5 ml), followed by the addition of 60% sodium hydride (0.075 g). After the evolution of hydrogen was ceased, 2-fluoroethyl bromide (230 μl) was added thereto, and then heated under reflux for 8 hr. After the reaction solution was cooled to room temperature, it was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.582 g of 1-(4-ethylpiperazin-1-yl)-3-[4-(2-fluoroethoxy)phenyl]isoquinoline as a white powder. The compound was converted into a hydrochloride in a conventional manner, to give the title compound as a yellow powder.

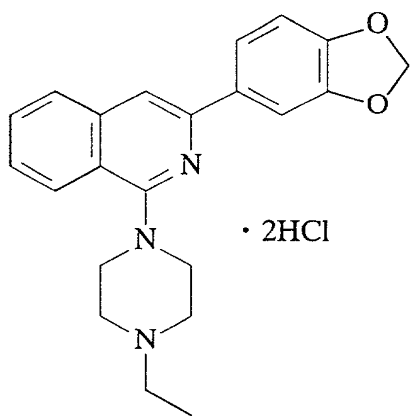
Hydrochloride:

m.p.; 223-224°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.4Hz,3H), 3.21-3.27(m,2H), 3.31-3.39(m,2H), 3.50(br-t,2H), 3.63(br-d,2H), 3.99(br-d,2H), 4.41(dt,J=4.0,30.0Hz,2H), 4.79(dt,J=4.0,48.0Hz,2H), 7.11(d,J=8.8Hz,2H), 7.58(br-t,1H), 7.73(br-t,1H), 7.96(d,J=8.0Hz,1H), 8.02(s,1H), 8.10(d,J=8.4Hz,1H), 8.16(d,J=8.8Hz,2H), 10.77(br-s,1H).

MS(FAB) m/z 380(M+H)$^+$.

Example 46 Synthesis of 3-(3,4-methylenedioxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



The free compound of the title compound was obtained (425 mg, yield; 94%) from 3-(3,4-methylenedioxyphenyl)-1-chloroisoquinoline (356 mg) and ethylpiperazine (10 ml) in the same manner as in Example 2. The resulting compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 3.20-3.26(m,2H), 3.30-3.38(m,2H), 3.52(t,J=12.0Hz,2H),

3.62(d,J=11.2Hz,2H), 3.99(d,J=13.2Hz,2H), 6.10(s,2H), 7.06(d,J=8.0Hz,1H), 7.58(t,J=8.0Hz,1H), 7.73(t,J=8.0Hz,1H), 7.75(d,J=2.0Hz,1H), 7.77(dd,J=8.0,2.0Hz,1H), 7.95(d,J=8.0Hz,1H), 8.01(s,1H), 8.09(d,J=8.0Hz,1H).

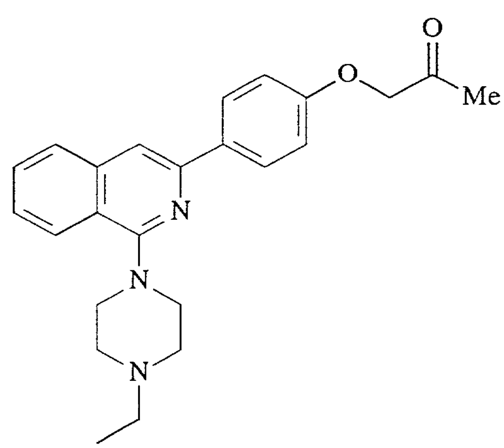
MS(FAB) m/z 362$(M+H)^+$.

m.p.; 223-227°C

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.75(br,4H), 3.58(br,4H), 6.02(s,2H), 6.91(d,J=8.4Hz,2H), 7.44(ddd,J=8.4,8.0,1.2Hz,1H), 7.57(ddd,J=8.4,8.0,1.2Hz,1H), 7.58(s,1H), 7.69(dd,J=8.4,1.6Hz,1H), 7.71(br,1H), 7.76(d,J=8.0Hz,1H), 8.06(d,J=8.4Hz,1H).

Example 47 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(4-acetonyloxyphenyl)isoquinoline

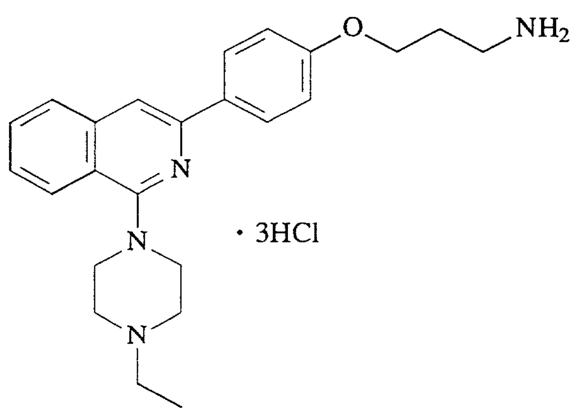


The title compound was obtained (346 mg, yield; 80%) as a yellow oil from 1-(1-ethylpiperazin-4-yl)-3-(4-hydroxyphenyl)isoquinoline (319 mg) and 1-bromo-2-propanone (100 mg), in the same manner as in Example 49.

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(3H,t,J=7.2Hz), 2.31(3H,s), 2.56(2H,q,J=7.2Hz), 2.76(4H,t,J=4.4Hz), 3.58(4H,t,J=4.4Hz), 4.59(2H,s), 6.98(2H,d,J=8.8Hz), 7.45(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.57(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.61(1H,s), 7.76(1H,d,J=8Hz), 8.06(1H,d,J=8Hz), 8.13(2H,d,J=8.8Hz).

ESI-Mass; 390(MH^+).

<u>Example 48</u> <u>Synthesis of 3-[4-(3-aminopropoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride</u>



Hydrazine monohydrate (0.16 ml) and ethanol (5 ml) were added to 3-[4-(3-phthalimidepropyloxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline (182 mg), and the resulting mixture was heated under reflux for 4 hr. Thereafter, the reaction solution was partitioned between chloroform and water. The resulting organic layer was washed with brine, dried and evaporated. The residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the free compound of the title compound as a yellow oil (482 mg, yield; 48%). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title

compound as yellow crystals.

Hydrochloride:

m.p.; 173-176°C

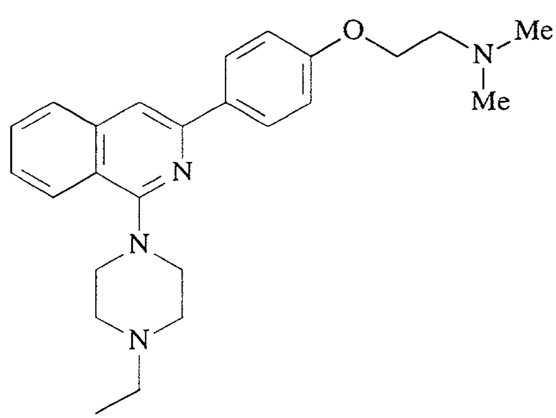
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 2.04-2.12(m,2H), 2.94-3.00(m,2H), 3.18-3.26(m,2H), 3.32-3.38(m,2H), 3.52-3.63(m,4H), 3.97(d,J=12.8Hz,2H), 4.16(t,J=6.4Hz,2H), 7.09(d,J=8.8Hz,2H), 7.58(t,J=8.0Hz,1H), 7.73(t,J=8.0Hz,1H), 7.96(d,J=8.0Hz,1H), 8.01(s,1H), 8.10(d,J=8.0Hz,1H), 8.13(br,2H), 8.17(d,J=8.8Hz,2H).

MS(FAB) m/z 391(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.04(s,2H), 2.12-2.18(m,2H), 2.55(q,J=7.2Hz,2H), 2.76(br,4H), 3.42(t,J=6.4Hz,2H), 3.58(br,4H), 4.12(t,J=6.0Hz,2H), 7.00(d,J=8.8Hz,2H), 7.43(t,J=8.0Hz,1H), 7.56(t,J=8.0Hz,1H), 7.61(s,1H), 7.76(d,J=8.0Hz,1H), 8.06(d,J=8.0Hz,1H), 8.10(d,J=8.8Hz,2H).

Example 49 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[4-(2-dimethylaminoethoxy)phenyl]isoquinoline



1-(1-Ethylpiperazin-4-yl)-3-(4-hydroxyphenyl)isoquinoline (500 mg) was dissolved in N,N-dimethylformamide (10 ml), followed by the addition of 60% sodium hydride (144 mg) under ice-cooling, and the resulting mixture was stirred at room temperature for 45 min. After the reaction solution was ice-cooled again, 2-dimethylaminomethyl chloride hydrochloride (259 mg) was added thereto, and the mixture was stirred at room temperature for overnight. The reaction mixture was thereafter partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The residue was purified by (NH) silica gel column chromatography (methylene chloride/methanol system), and the resulting product was converted into a hydrochloride in a conventional manner and recrystallized from hydrous ethanol/ether, to give the hydrochloride of the title compound as yellow crystals (595 mg, yield; 80%).

Hydrochloride:

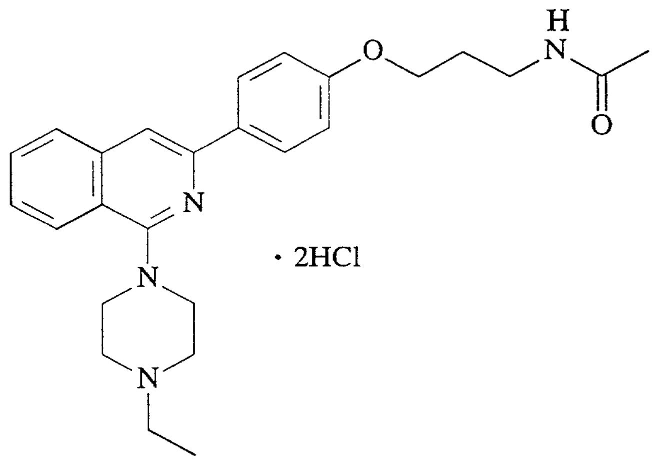
m.p.; 153-158°C

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.32(3H,t,J=7.2Hz), 2.83(3H,s), 2.84(3H,s), 3.19(2H,q,J=7.2Hz), 3.21(1H,q,J=7.2Hz), 3.30(1H,t,J=13.6Hz), 3.33(1H,t,J=13.6Hz), 3.51(1H,t,J=5.2Hz), 3.48-3.51(1H,m), 3.59(2H,d,J=13.6Hz), 3.95(2H,d,J=13.6Hz), 4.43(2H,t,J=5.2Hz), 7.13(2H,d,J=8.8Hz), 7.56(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.71(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.94(1H,d,J=8Hz), 8.08(1H,d,J=8Hz), 8.17(2H,d,J=8.8Hz),

10.70(1H,br-s), 11.32(1H,br-s).

ESI-Mass; 405(MH^+).

Example 50 Synthesis of 3-[4-(3-acetamidepropoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



Acetic anhydride (0.06 ml), pyridine (0.07 ml) and THF (4 ml) were added to 3-[4-(3-aminopropoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline (182 mg), and the mixture was stirred at room temperature overnight. The reaction mixture was thereafter partitioned between ethyl acetate and water. The resulting organic phase was washed with brine, dried and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give a yellow oil (8 mg, yield; 4%). The oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

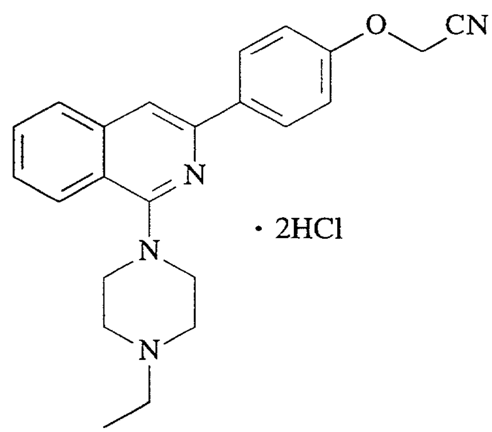
Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.00(s,3H), 2.58(q,J=7.2Hz,2H), 2.78(br,4H), 3.49(q,J=6.0Hz,2H),

3.60(br,4H), 3.73-3.76(m,1H), 4.12(t,J=6.0Hz,2H), 6.90(d,J=8.8Hz,2H), 7.43(dt,J=8.0,1.2Hz,1H), 7.57(dt,J=8.0,1.2Hz,1H), 7.62(s,1H), 7.77(d,J=8.0Hz,1H), 8.06(d,J=8.0Hz,1H), 8.12(d,J=8.8Hz,2H).

MS(FAB) m/z 433$(M+H)^+$.

Example 51 Synthesis of 3-(4-cyanomethoxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



To a solution of 1-(4-ethylpiperazin-1-yl)-3-(4-hydroxyphenyl)isoquinoline (0.30 g) obtained in Example 7 in tetrahydrofuran (15 ml) was added 60% sodium hydride (36 mg) at room temperature. After the evolution of hydrogen was ceased, bromoacetonitrile (0.11 g) was added thereto, and the resulting mixture was reacted at room temperature for 12 hr. Ethyl acetate and an aqueous solution of ammonium chloride were added to the reaction solution. The resulting organic layer was then separated, washed with water, dried and concentrated. To the resulting residue, ethanol and a 2N aqueous solution of hydrochloric acid were added, reacted at 50°C for 30 min, followed by evaporation. The resulting residue was

partitioned between ethyl acetate and water. The resulting organic layer was washed with water and brine, and dried. The solvent was removed, and the resulting residue was purified by NH-silica gel column chromatography (ethyl acetate/hexane system), to give the free compound of the title compound as a pale yellow oil. The free compound was converted into a hydrochloride in a conventional manner, to give 0.17 g of the title compound as a yellow powder.

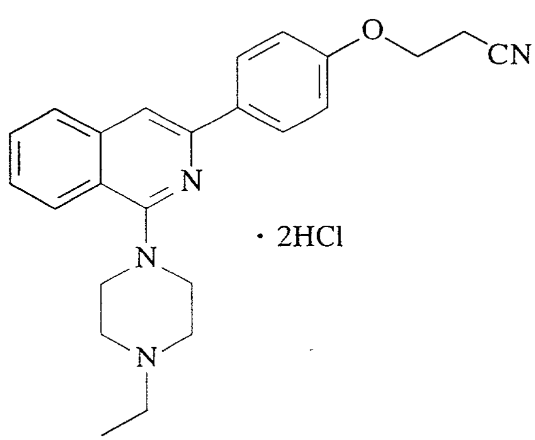
Hydrochloride:

m.p.; 123-125°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 3.19-3.41(m,4H), 3.48-3.65(m,4H), 4.00(br-d,2H), 5.27(s,2H), 7.22(d,J=8.8Hz,2H), 7.60(br-t,1H), 7.74(br-t,1H), 7.97(d,J=8.0Hz,1H), 8.06(s,1H), 8.11(d,J=8.0Hz,1H), 8.22(d,J=8.8Hz,2H), 11.11(m,1H).

MS(ESI) m/z 373(M+H)$^+$.

Example 52 Synthesis of 3-[4-(2-cyanoethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



To a solution of 1-(4-ethylpiperazin-1-yl)-3-(4-

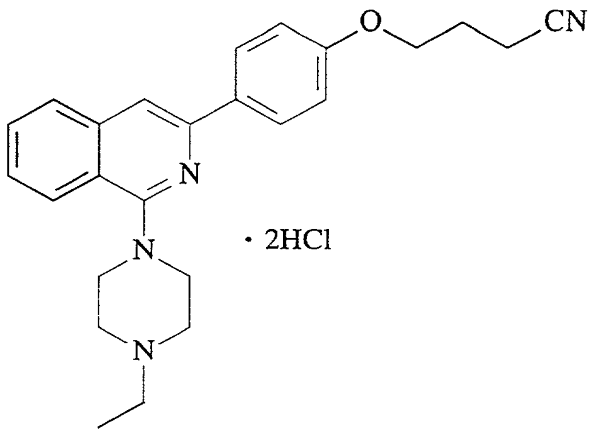
hydroxyphenyl)isoquinoline (0.30 g) obtaiend in Example 7 in acrylonitrile (10 ml) was added hydroxylated N-benzyltrimethylammonium (0.5 g), and the resulting mixture was reacted. The reaction solution was evaporated, and the resulting residue was partitioned between ethyl acetate and water. The resulting organic layer was washed with water and brine, and dried. The solvent was remove, and the resulting residue was purified by NH-silica gel column chromatography (ethyl acetate/hexane system), to give the free compound of the title compound as a pale yellow oil. The free compound was converted into a hydrochloride in a conventional manner, to give the title compound as a yellow powder (0.24 g).

Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.37(t,J=7.2Hz,3H), 2.98(t,J=5.2Hz,2H), 3.25-3.55(m,6H), 3.70(br-d,2H), 4.04(br-d,2H), 4.17(t,J=5.2Hz,2H), 6.85(d,J=8.0Hz,2H), 7.36(s,1H), 7.55(d,J=8.0Hz,2H), 7.63(br-t,1H), 7.68(br-d,1H), 7.75(br-t,1H), 7.97(d,J=8.0Hz,2H).

MS(ESI) m/z 387(M+H)$^+$.

Example 53 Synthesis of 3-[4-(3-cyanopropoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



To a solution of 1-(4-ethylpiperazin-1-yl)-3-(4-hydroxyphenyl)isoquinoline (0.30 g) obtained in Example 7 in tetrahydrofuran (15 ml) was added 60% sodium hydride (36 mg) at room temperature. After the evolution of hydrogen was ceased, bromopropionitrile (0.14 g) was added thereto, and the resulting mixture was reacted at room temperature for 12 hr. Ethyl acetate and an aqueous solution of ammonium chloride were added to the reaction solution, and the resulting organic layer was then separated, washed with water, dried and concentrated. To the resulting residue were added ethanol and a 2N aqueous solution of hydrochloric acid, and the resulting mixture was reacted at 50°C for 30 min, followed by the evaporation. The resulting residue was partitioned between ethyl acetate and water. The resulting organic layer was washed with water and brine, and dried. The solvent was removed, and the resulting residue was purified by NH-silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a pale yellow oil. The oil was converted into a hydrochloride in a conventional manner, to give 0.12 g of the title compound

as a yellow powder.

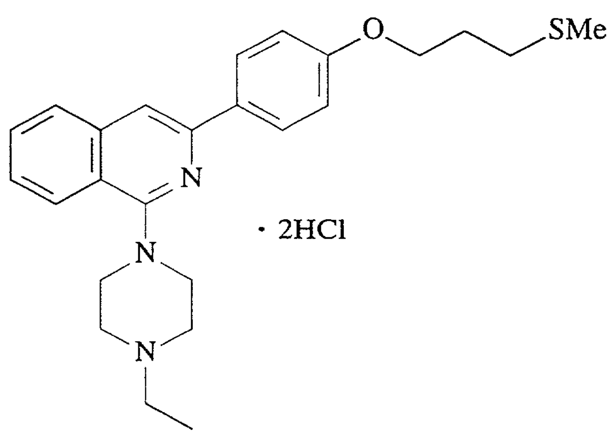
Hydrochloride:

m.p.; 144-146°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 2.02-2.11(m,2H), 2.70(t,J=7.2Hz,2H), 3.18-3.27(m,2H), 3.34(q,J=7.2Hz,2H), 3.50-3.65(m,4H), 3.98(br-d,2H), 4.12(t,J=6.0Hz,2H), 7.09(d,J=8.8Hz,2H), 7.58(br-t,1H), 7.73(br-t,1H), 7.96(d,J=8.0Hz,1H), 8.01(s,1H), 8.10(d,J=8.0Hz,1H), 8.16(d,J=8.8Hz,2H), 11.22(m,1H).

MS(ESI) m/z 401(M+H)$^+$.

<u>Example 54 Synthesis of 3-[4-(3-methylthiopropoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride</u>



THF (6 ml), DMF (6 ml) and sodium thiomethoxide (270 mg) were added to 3-[4-(3-methanesulfonate propoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline, and then reacted at 80 °C for 10 hr. The reaction solution was partitioned between ethyl acetate and water, and the organic layer was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography, to give an oil (258 mg, yield;

81%). The oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as a yellow amorphous.

Hydrochloride (amorphous):

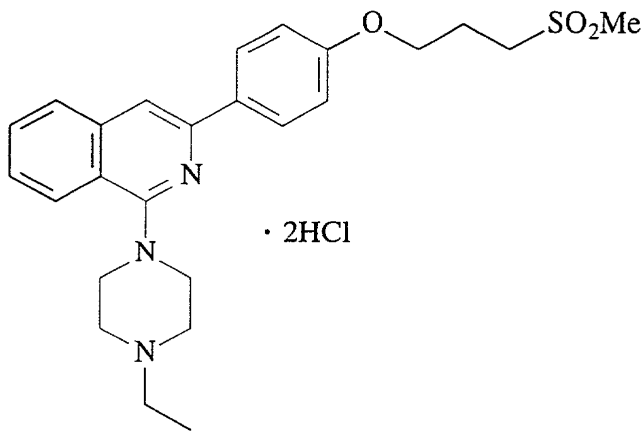
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 1.88-2.05(m,2H), 2.09(s,3H), 2.65(t,J=7.2Hz,2H), 3.20-3.28(m,2H), 3.30-3.40(m,2H), 3.46-3.53(m,2H), 3.63(d,J=11.2Hz,2H), 3.99(d,J=13.6Hz,2H), 4.13(t,J=6.4Hz,2H), 7.07(d,J=8.8Hz,2H), 7.57(t,J=8.4,Hz,1H), 7.72(t,J=8.4Hz,1H), 7.96(d,J=8.4Hz,1H), 8.00(s,1H), 8.09(d,J=8.4Hz,1H), 8.14(d,J=8.8Hz,2H).

MS(FAB) m/z 422$(M+H)^+$

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.08-2.13(m,2H), 2.14(s,3H), 2.55(q,J=7.2Hz,2H), 2.72(t,J=7.2Hz,2H), 2.77(br,4H), 3.58(br,4H), 4.13(t,J=6.0Hz,2H), 6.99(d,J=8.8Hz,2H), 7.43(ddd,J=8.4,8.0,1.2Hz,1H), 7.56(ddd,J=8.4,8.0,1.2Hz,1H), 7.61(s,1H), 7.76(d,J=8.0Hz,1H), 8.05(d,J=8.4Hz,1H), 8.11(d,J=8.8Hz,2H).

Example 55 Synthesis of 3-[4-(3-Methylsulfonpropoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners as in Examples 161-2 and then 20, the free compound of the title compound was obtained (47 mg, yield; 31%) from 1-bromo-4-(3-methylsulfonpropoxy)benzene (855 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (107 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 113-115°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 2.15-2.22(m,2H), 3.04(s,3H), 3.20-3.28(m,2H), 3.29-3.38(m,4H), 3.49(t,J=12.4Hz,2H), 3.63(d,J=12.0Hz,2H), 3.99(d,J=13.6Hz,2H), 4.17(t,J=6.4Hz,2H), 7.08(d,J=8.8Hz,2H), 7.58(t,J=8.0,Hz,1H), 7.73(t,J=8.0Hz,1H), 7.95(d,J=8.0Hz,1H), 8.01(s,1H), 8.10(d,J=8.0Hz,1H), 8.16(d,J=8.8Hz,2H).

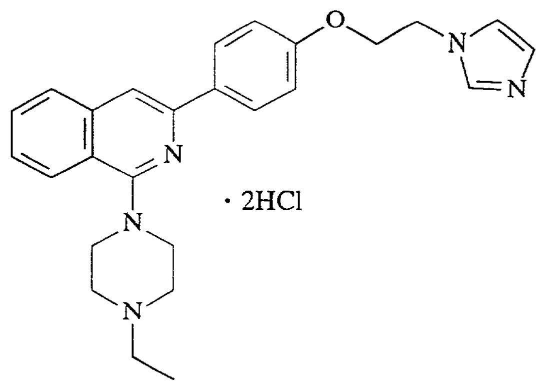
MS(FAB) m/z 454$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.11(t,J=7.2Hz,3H), 2.25-2.35(m,2H), 2.50(q,J=7.2Hz,2H), 2.70(br,4H), 2.89(s,3H),

3.19-3.23(m,2H), 3.52(br,4H), 4.10(t,J=6.0Hz,2H), 6.90(d,J=8.8Hz,2H), 7.36(ddd,J=8.4,8.0,1.2Hz,1H), 7.50(ddd,J=8.4,8.0,1.2Hz,1H), 7.54(s,1H), 7.69(d,J=8.0Hz,1H), 7.98(d,J=8.4Hz,1H), 8.04(d,J=8.8Hz,2H).

Example 56 Synthesis of 3-{4-[2-(1-imidazonyl)ethoxy]phenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



3-[4-(2-Methanesulfonate ethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline (768 mg) was dissolved in DMF (10 ml), to which were then added 60% sodium hydride (221 mg) and imidazole (575 mg), and the resulting mixture was reacted at 60°C overnight. The reaction solution was partitioned between ethyl acetate and water, and the resulting organic layer was washed with brine, dried and evaporated. Then, the resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give a yellow oil (576 mg, yield; 80%). The oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 3.18-3.26(m,2H), 3.30-3.40(m,2H), 3.53-3.62(m,2H), 3.94(d,J=13.2Hz,2H), 4.48(d,J=5.2Hz,2H), 4.67(d,J=5.2Hz,1H), 7.09(d,J=8.8Hz,2H), 7.58(t,J=8.0Hz,1H), 7.72(s,1H), 7.73(t,J=8.0Hz,1H), 7.89(s,1H), 7.96(d,J=8.0Hz,1H), 8.01(s,1H), 8.10(d,J=8.0Hz,1H), 8.16(d,J=8.8Hz,2H), 9.30(s,1H).

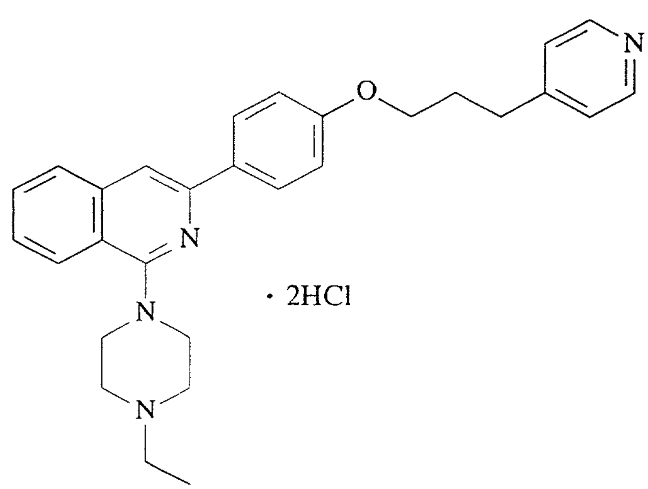
MS(FAB) m/z 428$(M+H)^+$.

m.p.; 160-162°C

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.77(br,4H), 3.58(br,4H), 4.27-4.30(m,2H), 4.36-4.38(m,2H), 4.28-4.30(m,2H), 6.96(d,J=8.8Hz,2H), 7.07-7.09(m,2H), 7.44(dt,J=8.0,1.2Hz,1H), 7.57(dt,J=8.0,1.2Hz,1H), 7.61(s,1H), 7.62(br,1H), 7.77(d,J=8.0Hz,1H), 8.06(d,J=8.0Hz,1H), 8.11(d,J=8.8Hz,2H).

Example 57 Synthesis of 3-{4-[3-(4-pyridyl)propoxy]phenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



The free compound of the title compound was obtained (333 mg, yield; 76%) from 3-(4-hydroxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline (322 mg) and 2-(3-methanesulfonate propyl)pyridine (417 mg), in the same manner as in Example 51. The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 129-131°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 2.16-2.24(m,2H), 3.10(t,J=7.2Hz,2H), 3.20-3.26(m,2H), 3.30-3.39(m,2H), 3.46-3.56(m,2H), 3.62(d,J=11.2Hz,2H), 3.97(d,J=13.2Hz,2H), 4.11(t,J=6.0Hz,2H), 7.04(d,J=8.8Hz,2H), 7.58(t,J=8.0Hz,1H), 7.73(t,J=8.0Hz,1H), 7.96(d,J=8.0Hz,1H), 8.00(s,1H), 8.02(d,J=6.8Hz,2H), 8.10(d,J=8.0Hz,1H), 8.15(d,J=8.8Hz,2H), 8.85(d,J=6.8Hz,2H).

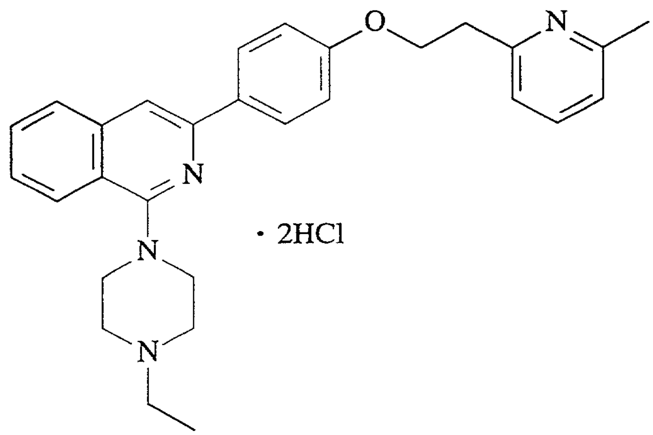
MS(FAB) m/z 453(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.11-2.18(m,2H), 2.56(q,J=7.2Hz,2H), 2.76(br,4H), 2.85(t,J=7.6Hz,2H), 3.58(br,4H), 4.03(t,J=6.0Hz,2H), 6.98(d,J=8.4Hz,2H), 7.16(d,J=4.8Hz,2H), 7.43(t,J=8.0Hz,1H), 7.57(t,J=8.0Hz,1H), 7.62(s,1H), 7.76(d,J=8.0Hz,1H), 8.06(d,J=8.0Hz,1H), 8.11(d,J=8.4Hz,2H), 8.51(d,J=4.8Hz,1H).

Example 58 Synthesis of 3-{4-[2-(2-methylpyridin-5-yl)ethoxy]phenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline

hydrochloride



DMF (10 ml), potassium carbonate (897 mg) and 2-methyl-5-(2-methanesulfonate ethyl)pyridine (558 mg) were added to 3-(4-hydroxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline (432 mg), and the resulting mixture was reacted at 100°C for 3 hr. The reaction solution was thereafter partitioned between ethyl acetate and water, and the resulting organic layer was washed with brine, dried and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give a yellow oil (268 mg, yield; 46%). The oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 136-138°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 2.81(s,3H), 3.18-3.26(m,2H), 3.30-3.38(m,2H), 3.53-3.62(m,4H), 3.95(t,J=13.2Hz,4H), 4.52(t,J=6.4Hz,2H), 7.09(d,J=8.8Hz,2H), 7.58(t,J=8.0Hz,1H), 7.73(t,J=8.0Hz,1H), 7.81(d,J=8.0Hz,1H),

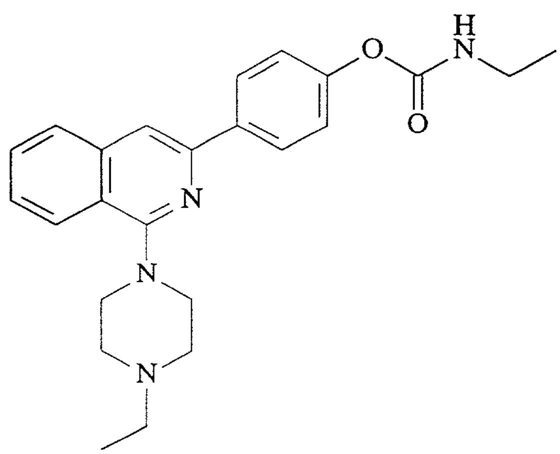
7.90(d,J=8.0Hz,1H), 7.96(d,J=8.0Hz,1H), 8.01(s,1H), 8.10(d,J=8.0Hz,1H), 8.15(d,J=8.8Hz,2H), 8.44(t,J=8.0Hz,1H).

MS(FAB) m/z 453$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.55(s,3H), 2.56(q,J=7.2Hz,2H), 2.75(br,4H), 3.26(t,J=6.8Hz,2H), 3.58(br,4H), 4.41(t,J=6.8Hz,2H), 6.99(d,J=8.8Hz,2H), 7.00-7.03(m,1H), 7.10(d,J=8.0Hz,1H), 7.42(ddd,J=8.4,8.0,1.2Hz,1H), 7.50(d,J=8.0Hz,1H), 7.56(ddd,J=8.4,8.0,1.2Hz,1H), 7.60(s,1H), 7.75(d,J=8.0Hz,1H), 8.05(d,J=8.4Hz,1H), 8.09(d,J=8.8Hz,2H).

Example 59 Synthesis of 1-(1-Ethylpiperazin-4-yl)-3-[4-(N-ethylcarbamyl)phenyl]isoquinoline



1-(1-Ethylpiperazin-4-yl)-3-(4-hydroxyphenyl)isoquinoline (333 mg) was dissolved in tetrahydrofuran (5 ml), ethyl isocyanate (800 ml) was added thereto, and then the mixture was stirred at room temperature for 3 hr. The reaction mixture was evaporated. The resulting residue was purified by silica gel column chromatography

(methylene chloride/methanol system), and then recrystallized from ethyl acetate/hexane, to give the free compound of the title compound. The free compound was converted into a hydrochloride in a conventional manner, which was then recrystallized (from ethanol/isopropyl ether), to give the hydrochloride of the title compound as yellow crystals (313 mg, yield; 70%).

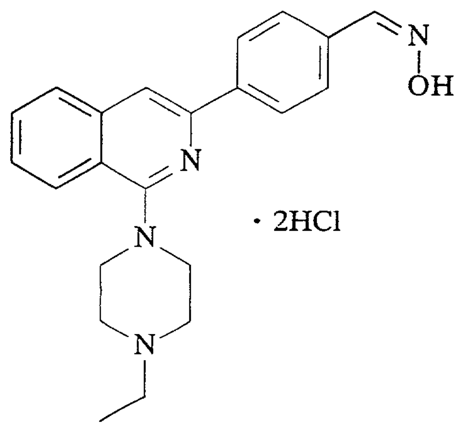
Hydrochloride:

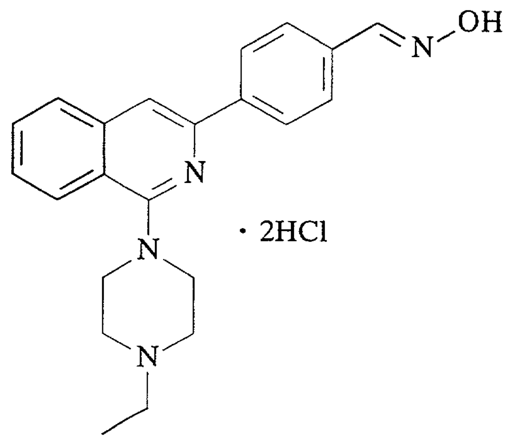
m.p.; 146-150°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.08(3H,t,J=7.2Hz), 1.30(3H,t,J=7.2Hz), 3.05-3.14(2H,m), 3.16-3.24(2H,m), 3.31(1H,t,J=11.6Hz), 3.34(1H,t,J=11.6Hz), 3.49(2H,t,J=13.2Hz), 3.59(2H,d,J=11.6Hz), 3.98(2H,d,J=13.2Hz), 7.21(2H,d,J=8.8Hz), 7.58(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.72(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.79(1H,t,J=5.6Hz), 7.96(1H,d,J=8Hz), 8.05(1H,s), 8.09(1H,d,J=8Hz), 8.17(2H,d,J=8.8Hz), 10.82(1H,br-s).

ESI-Mass; 405(MH$^+$).

Examples 60 and 61 Synthesis of (Z)-1-(4-Ethylpiperazin-1-yl)-3-(4-hydroxyiminomethylphenyl)isoquinoline and (E)-1-(4-Ethylpiperazin-1-yl)-3-(4-hydroxyiminomethylphenyl)isoquinoline





1-(4-Ethylpiperazin-1-yl)-3-(4-formylphenyl)isoquinoline (3.00 g) obtained in Example 17-5 was reacted with hydroxylamine hydrochloride (0.90 g) and sodium acetate (1.10 g) in ethanol (50 ml) at 60°C for 2 hr. The reaction solution was evaporated, and then the resulting residue was extracted in methylene chloride, washed with brine and dried. The solvent was removed, and the resulting residue was isolated and purified by silica gel column chromatography (methylene chloride/methanol system), to give (Z)-1-(4-ethylpiperazin-1-yl)-3-(4-hydroxyiminomethylphenyl)isoquinoline (1.01 g) and (E)-1-(4-ethylpiperazin-1-yl)-3-(4-hydroxyiminomethylphenyl)isoquinoline (1.52 g), both as yellow solids. 0.30 g each of the compounds was converted into a hydrochloride in a conventional manner, to give the hydrochlorides of the title compounds as yellow powders (0.32 g and 0.35g, respectively).

(Example 60)

(Z)-1-(4-Ethylpiperazin-1-yl)-3-(4-

hydroxyiminomethylphenyl)isoquinoline hydrochloride

m.p.; 239°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 3.18-3.28(m,2H), 3.29-3.41(m,2H), 3.50-3.66(m,4H), 3.98-4.06(m,2H), 7.60-7.66(m,1H), 7.74(d,J=8.4Hz,2H), 7.73-7.79(m,1H), 8.00(d,J=8.4Hz,1H), 8.13(d,J=8.8Hz,1H), 8.15(s,1H), 8.21(s,1H), 8.25(d,J=8.4Hz,2H), 11.13(m,1H).

MS(FAB) m/z 361 $(M+H)^+$.

(Example 61)

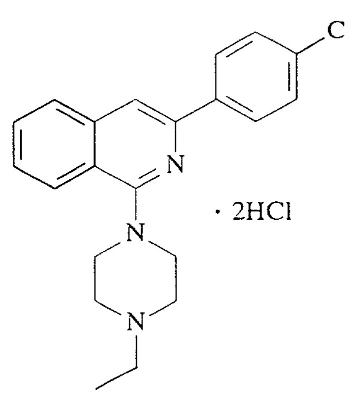
(E)-1-(4-Ethylpiperazin-1-yl)-3-(4-hydroxyiminomethylphenyl)isoquinoline hydrochloride

m.p.; 243°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.32(t,J=7.2Hz,3H), 3.19-3.29(m,2H), 3.29-3.41(m,2H), 3.48-3.67(m,4H), 3.97-4.06(m,2H), 7.60-7.66(m,1H), 7.73(d,J=8.4Hz,2H), 7.72-7.79(m,1H), 8.00(d,J=8.4Hz,1H), 8.13(d,J=8.8Hz,1H), 8.15(s,1H), 8.21(s,1H), 8.25(d,J=8.4Hz,2H), 10.98(m,1H).

MS(FAB) m/z 361$(M+H)^+$.

Example 62 Synthesis of 3-(4-cyanophenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



(E,Z)-1-(4-Ethylpiperazin-1-yl)-3-(4-hydroxyiminomethylphenyl)isoquinoline (1.92 g) obtained in Example 61 was reacted with acetic anhydride in acetic acid at 120°C for 1.5 hr. The reaction solution was evaporated, and to the resulting residue were then added ethyl acetate and a 10% aqueous solution of potassium carbonate, and the mixture was then extracted with ethyl acetate. The resulting organic layer was washed with water and brine, dried and concentrated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 1.78 g of the free compound of the title compound. 0.28 g of the resulting free compound was converted into a hydrochloride in a conventional manner, to give 0.23 g of the title compound as a yellow powder.

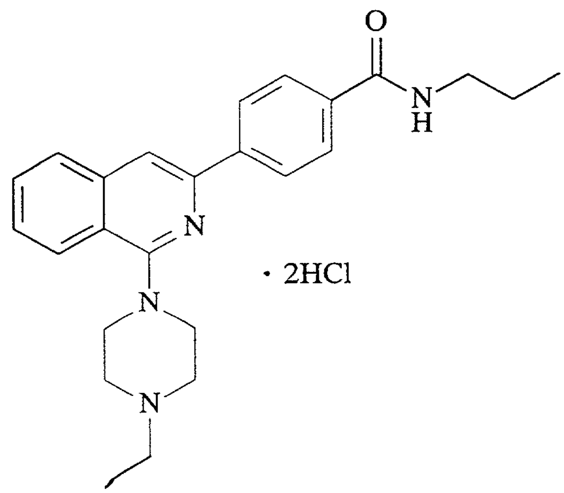
Hydrochloride:

m.p.; 241°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 3.18-3.28(m,2H), 3.29-3.41(m,2H), 3.51-3.66(m,4H), 3.99-4.07(m,2H), 7.65-7.71(m,1H), 7.77-7.83(m,1H), 7.99(d,J=8.8Hz,2H), 8.03(d,J=8.4Hz,1H), 8.29(s,1H), 8.41(d,J=8.8Hz,2H), 11.20(m,1H).

MS(FAB) m/z 343(M+H)$^+$.

<u>Example 63 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(4-N-propylaminocarbonylphenyl)isoquinoline hydrochloride</u>



(4-N-Propylaminocarbonylphenyl)tributylstannum (1.350 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.820 g) were reacted in the presence of tetrakistriphenylphosphine (0.116 g) in xylene (20 ml) in nitrogen atmosphere overnight. After cooling, the reaction solution was filtered. The resulting filtrate was extracted with a 5N aqueous solution of hydrochloric acid. The resulting aqueous layer was basified with a 5N aqueous solution of sodium hydroxide, and then extracted with ethyl acetate. The resulting organic layer was washed with water and brine, dried and concentrated. The resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.578 g of the free compound of the title compound as a pale yellow solid.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.02(t,J=7.2Hz,3H), 1.18(t,J=7.2Hz,3H), 1.63-1.73(m,2H), 2.56(q,J=7.2Hz,2H), 2.77(br-t,2H), 3.46(dt,J=6.0,7.2Hz,2H), 3.60(br-t,4H), 6.19(br-t,1H), 7.49(br-t,1H), 7.61(br-t,1H), 7.75(s,1H),

7.81(d,J=8.0Hz,1H), 7.86(d,J=8.8Hz,2H), 8.09(d,J=7.6Hz,1H), 8.24(d,J=8.8Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/ether, to give the title compound as a pale yellow powder.

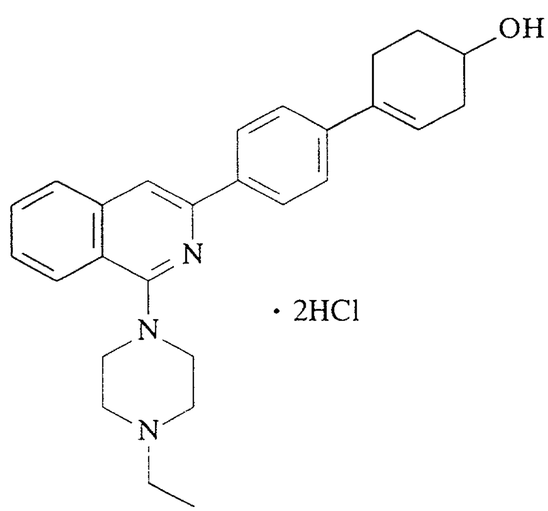
Hydrochloride:

m.p.; 149-150°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.92(t,J=7.2Hz,3H), 1.33(t,J=7.2Hz,3H), 1.57(dq,J=7.2Hz,2H), 3.21-3.28(m,2H), 3.32-3.40(m,2H), 3.53(br-t,2H), 3.64(br-d,2H), 4.03(br-d,2H), 7.65(br-t,1H), 7.77(br-t,1H), 7.99(d,J=8.4Hz,2H), 8.02(d,J=7.6Hz,1H), 8.14(d,J=8.4Hz,2H), 8.21(s,1H), 8.28(d,J=8.4Hz,2H), 8.56(t,J=7.2Hz,1H), 10.87(br-s,1H).

MS(FAB) m/z 403(M+H)$^+$.

Example 64 Synthesis of 3-[4-(4-hydroxy-1-cyclohexen-1-yl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners as in Examples 161-2 and then 20, an oil was obtained from 1-bromo-4-(4-acetoxy-1-cyclohexen-1-yl)benzene (477 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (200 mg). Methanol (10 ml) and a 1N aqueous solution of sodium hydroxide (1 ml) were added to the resulting oil, and then the mixture was heated under reflux for 1 hr. The reaction solution was partitioned between ethyl acetate and water, and the resulting organic layer was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system), to give a colorless oil (175 mg, yield; 68%). The oil was converted into a hydrochloride in a conventional manner, to give hydrochloride of the title compound as white crystals.

Hydrochloride:

Melting point; 164-166°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 1.63(br,1H), 2.44(br,2H), 3.24(t,J=6.0Hz,2H), 3.35-3.40(m,2H), 3.45-3.50(m,2H), 3.63(d,J=11.6Hz,2H), 3.82(br,4H), 4.00(d,J=14.8Hz,2H), 6.17(s,1H), 7.55(d,J=8.4Hz,2H), 7.61(t,J=8.0Hz,1H), 7.74(t,J=8.0Hz,1H), 7.99(d,J=8.0Hz,1H), 8.10(s,1H), 8.11(d,J=8.0Hz,1H), 8.16(d,J=8.4Hz,2H).

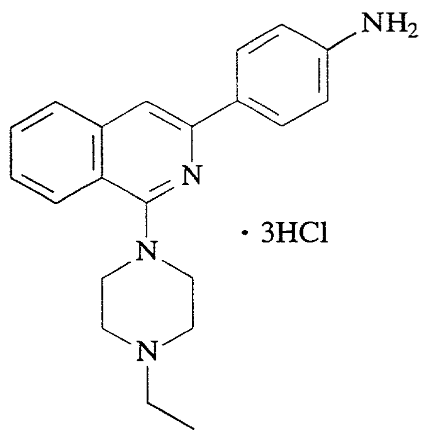
MS(FAB) m/z 414(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.19(t,J=7.6Hz,3H), 1.86-1.89(m,1H), 2.05-2.10(m,1H), 2.24-2.31(m,1H), 2.55-2.66(m,3H), 2.57(q,J=7.6Hz,2H), 2.77(br,4H), 3.60(br,4H), 4.06-4.14(m,1H),

6.17(s,1H)、7.46(t,J=8.4Hz,1H)、7.50(d,J=8.4Hz,2H)、7.59(t,J=8.4Hz,1H)、7.76(s,1H)、7.79(d,J=8.4Hz,1H)、8.08(d,J=8.4Hz,1H)、8.14(d,J=8.4Hz,2H).

Example 65 Synthesis of 3-(4-aminophenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



Ethanol (30 ml) and a 2N aqueous solution of hydrochloric acid (4 ml) were added to 3-(4-acetamidephenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline, and the resulting mixture was stirred at 80°C for 4 hr. The reaction solution was basified with a 1N aqueous solution of sodium hydroxide, and then extracted with ethyl acetate. The resulting organic layer was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography, to give an oil (71 mg, yield; 7%). The oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 267-268°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.35(t,J=7.2Hz,3H), 3.20-

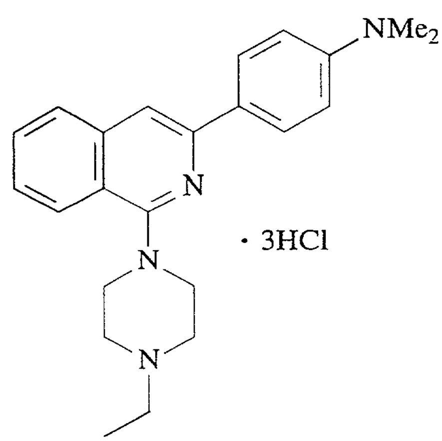
3.26(m,2H), 3.30-3.40(m,2H), 3.56-3.62(m,4H), 4.02(d,J=13.2Hz,2H), 7.54(d,J=8.4Hz,2H), 7.64(t,J=8.0,Hz,1H), 7.77(t,J=8.0Hz,1H), 8.00(d,J=8.0Hz,1H), 8.13(s,1H), 8.14(d,J=8.0Hz,1H), 8.31(d,J=8.4Hz,2H).

MS(FAB) m/z 333$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.75(br,4H), 3.57(br,4H), 3.79(br,2H), 6.78(d,J=8.4Hz,2H), 7.49(t,J=8.0Hz,1H), 7.55(t,J=8.0Hz,1H), 7.57(s,1H), 7.74(d,J=8.0Hz,1H), 8.01(d,J=8.4Hz,2H), 8.04(d,J=8.0Hz,1H).

Example 66 Synthesis of 3-[4-(N,N-dimethylamino)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline dihydrochloride



According to the method of Example 10-1, 3-[4-(N,N-dimethylamino)phenyl]isoquinolin-1-one was obtained from N-methyl-o-toluamide (4.47 g) and 4-(N,N-dimethylamino)benzonitrile.

Subsequently, the resulting 3-[4-(N,N-dimethylamino)]isoquinolin-1-one (2.834 g) was added to

phosphorus oxychloride (25 ml), and the resulting mixture was heated at 110°C for 1.5 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water, an aqueous solution of sodium bicarbonate and brine, and dried over magnesium sulfate. The solvent was removed, and the resulting 1-chloro-3-[4-(N,N-dimethylamino)]isoquinoline was reacted with N-ethylpiperazine (35 ml) at 120°C for 5 hr. The reaction solution was evaporated, and the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was removed, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 2.687 g of the free compound of the title compound as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.4Hz,3H), 2.55(q,J=7.4Hz,2H), 2.75(br-t,4H), 3.02(s,6H), 3.58(br-t,4H), 6.82(d,J=8.8Hz,2H), 7.38(br-t,1H), 7.53(br-t,1H), 7.58(s,1H), 7.74(d,J=8.4Hz,1H), 8.04(d,J=8.4Hz,1H), 8.09(d,J=8.8Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give the title compound as a yellow powder.

Hydrochloride:

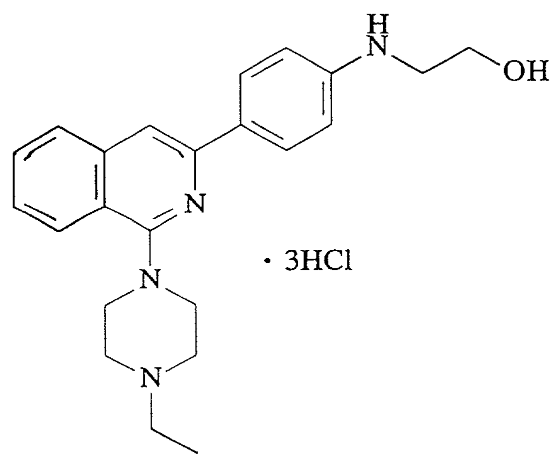
m.p.; 160-162°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 3.11(s,6H),

3.19-3.25(m,2H), 3.30-3.38(m,2H), 3.55-3.62(m,4H), 4.00(br-d,2H), 7.54(br-s,2H), 7.60(br-t,1H), 7.75(br-t,1H), 7.98(d,J=8.4Hz,1H), 8.07(s,1H), 8.11(d,J=8.0Hz,1H), 8.24(d,J=8.4Hz,2H), 11.31(br-s,1H).

MS(FAB) m/z 361$(M+H)^+$.

Example 67 Synthesis of 3-[4-(2-hydroxyethyl)aminophenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, an oil was obtained from 1-bromo-4-(2-acetoxyethyl)aminobenzene (905 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (266 mg). Ethanol (10 ml) and a 2N aqueous solution of hydrochloric acid (1 ml) were added to the resulting oil, and then the mixture was heated under reflux for 3 hr. The reaction solution was basified with a 1N aqueous solution of sodium hydroxide, and then extracted with ethyl acetate. The resulting organic layer was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography, to give an oil

(120 mg, yield; 38%). The oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as a yellow amorphous.

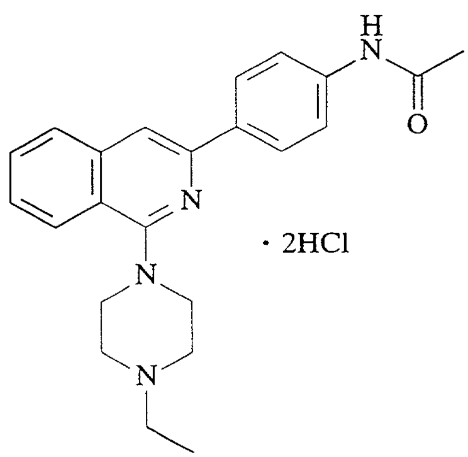
Hydrochloride (amorphous):

MS(FAB) m/z 377$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.76(br,4H), 3.39(t,J=5.2Hz,2H), 3.58(br,4H), 3.88(t,J=5.2Hz,2H), 6.75(d,J=8.8Hz,2H), 7.39(t,J=8.4Hz,1H), 7.44(d,J=8.4Hz,1H), 7.54(t,J=8.4Hz,1H), 7.57(s,1H), 7.73(d,J=8.4Hz,1H), 8.04(d,J=8.8Hz,2H).

<u>Example 68 Synthesis of 3-(4-acetamidephenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride</u>



In the same manners as in Example 20, the free compound of the title compound was obtained (1.09 g, yield; 40%) from from 1-bromo-4-acetoanilide (5.07 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (2.3 g). The free compound was converted into a hydrochloride in a conventional manner,

to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

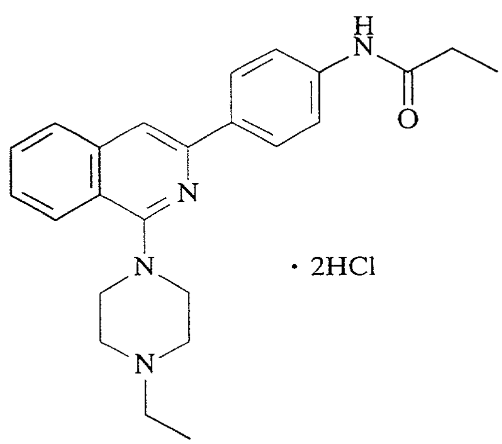
m.p.; 180-182°C

MS(FAB) m/z 375$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.20(t,J=7.2Hz,3H), 2.21(s,3H), 2.58(q,J=7.2Hz,2H), 2.80(br,4H), 3.62(br,4H), 7.45(t,J=8.0Hz,1H), 7.58(t,J=8.0Hz,1H), 7.61(d,J=8.8Hz,2H), 7.67(s,1H), 7.78(d,J=8.0Hz,1H), 8.06(d,J=8.0Hz,2H), 8.14(d,J=8.8Hz,2H).

<u>Example 69 Synthesis of 3-(4-ethylcarbonylaminophenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride</u>



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (520 mg, yield; 58%) from 1-bromo-4-ethylcarbonylaminobenzene (3.85 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (745 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title

compound as yellow crystals.

Hydrochloride:

m.p.; 176-178°C

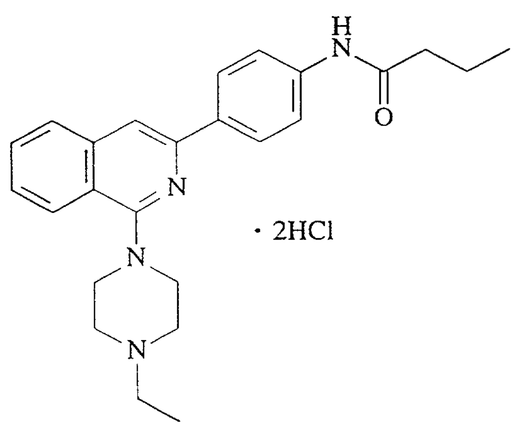
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.11(t,J=7.2Hz,3H), 1.33(t,J=7.2Hz,3H), 2.38(q,J=7.2Hz,2H), 3.20-3.25(m,2H), 3.32-3.39(m,4H), 3.52(t,J=12.4Hz,2H), 3.62(d,J=11.2Hz,2H), 7.58(t,J=8.0Hz,1H), 7.73(t,J=8.0Hz,1H), 7.75(d,J=8.8Hz,2H), 7.96(d,J=8.0Hz,1H), 8.03(s,1H), 8.10(d,J=8.0Hz,1H), 8.15(d,J=8.8Hz,2H), 10.10(s,1H).

MS(FAB) m/z 389(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 1.27(t,J=7.2Hz,3H), 2.42(q,J=7.2Hz,2H), 2.55(q,J=7.2Hz,2H), 2.75(t,J=4.4Hz,4H), 3.58(t,J=4.4Hz,4H), 7.44(ddd,J=8.4,8.0,1.2Hz,1H), 7.57(ddd,J=8.4,8.0,1.2Hz,1H), 7.63(d,J=8.4Hz,2H), 7.65(s,1H), 7.76(d,J=8.0Hz,1H), 8.06(d,J=8.4Hz,1H), 8.14(d,J=8.4Hz,2H).

Example 70 Synthesis of 3-(4-propylcarbonylaminophenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (604 mg, yield; 53%) from 1-bromo-4-propylcarbonylaminobenzene (4.13 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (913 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 170-172°C

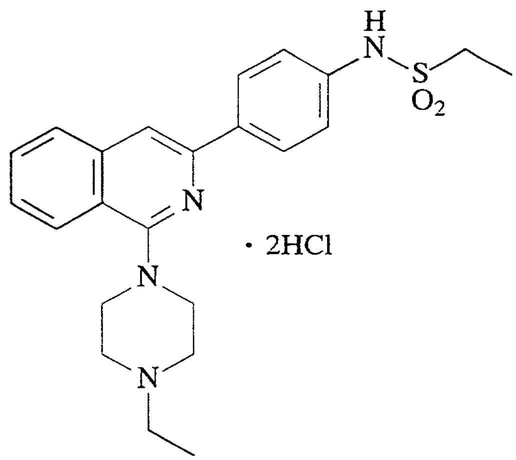
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.94(t,J=7.2Hz,3H), 1.34(t,J=7.2Hz,3H), 1.59-1.79(m,2H), 2.35(q,J=7.2Hz,2H), 3.20-3.25(m,2H), 3.30-3.40(m,4H), 3.54-3.63(m,4H), 4.00(d,J=13.6Hz,2H), 7.59(t,J=8.0Hz,1H), 7.73(t,J=8.0Hz,1H), 7.78(d,J=8.8Hz,2H), 7.96(d,J=8.0Hz,1H), 8.02(s,1H), 8.10(d,J=8.0Hz,1H), 8.14(d,J=8.8Hz,2H), 10.40(s,1H).

MS(FAB) m/z 403$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.03(t,J=7.2Hz,3H), 1.17(t,J=7.2Hz,3H), 1.72-1.82(m,2H), 2.37(t,J=7.2Hz,2H), 2.56(q,J=7.2Hz,2H), 2.76(t,J=4.0Hz,4H), 3.58(t,J=4.0Hz,4H), 7.45(dt,J=8.0,1.2Hz,1H), 7.57(dt,J=8.0,1.2Hz,1H), 7.63(d,J=8.4Hz,2H), 7.65(s,1H), 7.77(d,J=8.0Hz,1H), 8.06(d,J=8.0Hz,1H), 8.14(d,J=8.4Hz,2H).

Example 71 Synthesis of 3-(4-ethylsulfonylaminophenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (542 mg, yield; 63%) from 1-bromo-4-ethylsulfonylaminobenzene (3.95 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (648 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 198-201°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.22(t,J=7.2Hz,3H), 1.34(t,J=7.2Hz,3H), 3.15(q,J=7.2Hz,2H), 3.18-3.24(m,2H), 3.30-3.39(m,2H), 3.53-3.62(m,4H), 4.00(d,J=13.6Hz,2H), 7.36(d,J=8.8Hz,2H), 7.59(dt,J=8.0,1.2Hz,1H), 7.74(dt,J=8.0,1.2Hz,1H), 7.97(d,J=8.0Hz,1H), 8.02(s,1H), 8.10(d,J=8.0Hz,1H), 8.16(d,J=8.8Hz,2H), 10.05(s,1H).

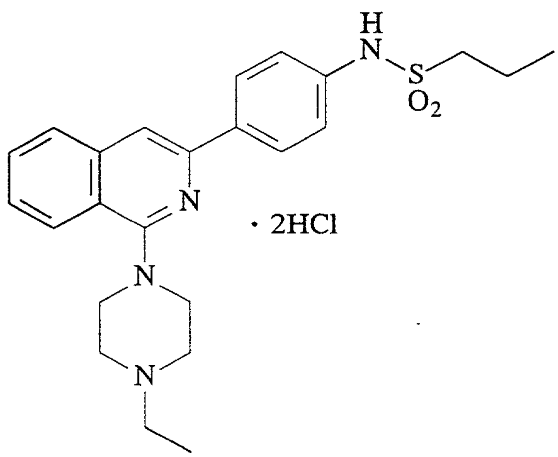
MS(FAB) m/z 425(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H),

1.39(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.77(br,4H), 3.18(q,J=7.2Hz,2H), 3.58(br,4H), 7.32(d,J=8.8Hz,2H), 7.46(ddd,J=8.4,8.0,1.2Hz,1H), 7.59(ddd,J=8.4,8.0,1.2Hz,1H), 7.65(s,1H), 7.78(d,J=8.0Hz,1H), 8.07(d,J=8.4Hz,1H), 8.15(d,J=8.8Hz,2H).

Example 72 Synthesis of 3-(4-propylsulfonylaminophenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (1.31 g, yield; 95%) from 1-bromo-4-propylsulfonylaminobenzene (4.69 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.0 g). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 163-165°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.95(t,J=7.2Hz,3H), 1.34(t,J=7.2Hz,3H), 1.66-1.76(m,2H), 3.11-3.15(m,2H), 3.20-

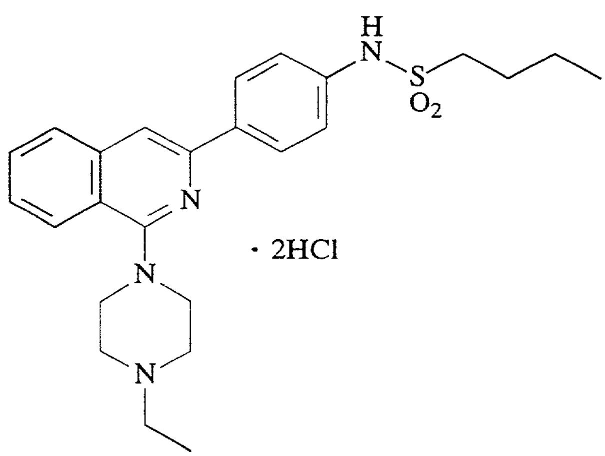
3.25(m,2H), 3.30-3.40(m,2H), 3.51-3.62(m,4H), 4.00(d,J=12.8Hz,2H), 7.35(d,J=8.8Hz,2H), 7.60(t,J=8.0Hz,1H), 7.74(t,J=8.0Hz,1H), 7.96(d,J=8.0Hz,1H), 8.02(s,1H), 8.11(d,J=8.0Hz,1H), 8.16(d,J=8.8Hz,2H).

MS(FAB) m/z 439$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.91(t,J=7.2Hz,3H), 1.18(t,J=7.2Hz,3H), 1.38-1.48(m,2H), 2.56(q,J=7.2Hz,2H), 2.77(br,4H), 3.11-3.16(m,2H), 3.59(br,4H), 7.31(t,J=8.8Hz,1H), 7.47(ddd,J=8.4,8.0,1.2Hz,1H), 7.59(ddd,J=8.4,8.0,1.2Hz,1H), 7.66(s,1H), 7.79(d,J=8.0Hz,1H), 8.08(d,J=8.4Hz,1H), 8.16(d,J=8.4Hz,2H).

Example 73 Synthesis of 3-(4-butylsulfonylaminophenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (828 mg, yield; 94%) from 1-bromo-4-butylsulfonylaminobenzene (3.51 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline

(620 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 160-163°C

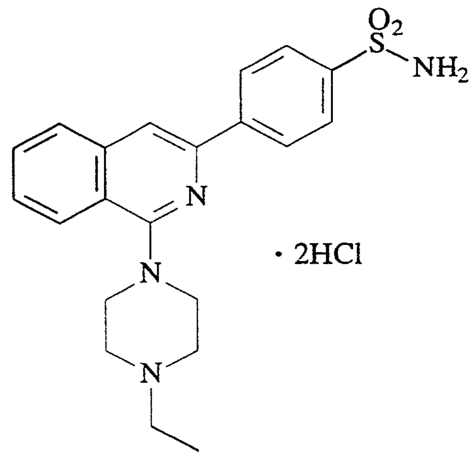
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.84(t,J=7.2Hz,3H), 1.32-1.39(m,5H), 1.64-1.70(m,2H), 3.13-3.17(m,2H), 3.22-3.24(m,2H), 3.33-3.38(m,2H), 3.53-3.62(m,4H), 4.00(d,J=13.2Hz,2H), 7.35(d,J=8.4Hz,2H), 7.60(t,J=8.0Hz,1H), 7.74(t,J=8.0Hz,1H), 7.97(d,J=8.0Hz,1H), 8.03(s,1H), 8.10(d,J=8.0Hz,1H), 8.17(d,J=8.4Hz,2H).

MS(FAB) m/z 453(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.03(t,J=7.6Hz,3H), 1.16-1.23(m,5H), 1.83-1.94(m,2H), 2.56(q,J=7.2Hz,2H), 2.76(br,4H), 3.01-3.13(m,2H), 3.59(br,4H), 7.31(d,J=8.4Hz,2H), 7.47(ddd,J=8.4,8.0,1.2Hz,1H), 7.59(ddd,J=8.4,8.0,1.2Hz,1H), 7.66(s,1H), 7.79(d,J=8.0Hz,1H), 8.07(d,J=8.4Hz,1H), 8.15(d,J=8.4Hz,2H).

Example 74 Synthesis of 3-(4-sulfonamidephenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (49 mg, yield; 7%) from 1-bromo-4-benzenesulfonamide (1.55 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (386 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

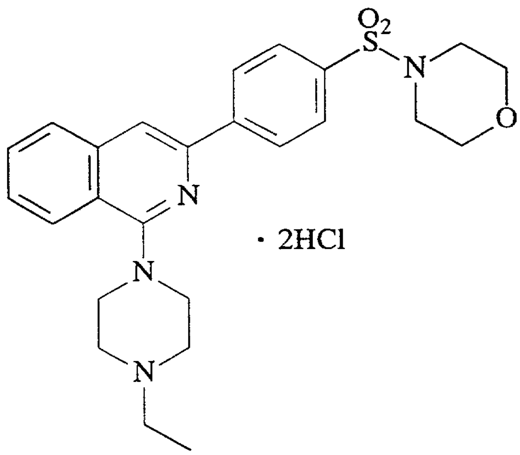
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 3.21-3.32(m,2H), 3.36-3.42(m,2H), 3.53(t,J=6.8Hz,2H), 3.63(d,J=12.0Hz,2H), 4.05(d,J=13.6Hz,2H), 7.45(s,2H), 7.67(t,J=8.0Hz,1H), 7.79(t,J=8.0,Hz,1H), 7.95(d,J=8.4Hz,2H), 8.02(d,J=8.0Hz,1H), 8.15(d,J=8.0Hz,1H), 8.23(s,1H), 8.38(d,J=8.4Hz,2H).

Free compound:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.08(t,J=7.2Hz,3H), 2.46(q,J=7.2Hz,2H), 2.68(br,4H), 3.47(br,4H), 7.42(s,2H), 7.62(ddd,J=8.4,8.0,1.2Hz,1H), 7.74(ddd,J=8.4,8.0,1.2Hz,1H),

7.94(d,J=8.4Hz,2H), 7.97(d,J=8.0Hz,1H), 8.09(d,J=8.0Hz,1H), 8.11(s,1H), 8.37(d,J=8.4Hz,2H).

Example 75 Synthesis of 3-[(4-morpholinyl)sulfonylphenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (620 mg, yield; 49%) from 4-(morpholinylsulfonyl)bromobenzene (2.63 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (872 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

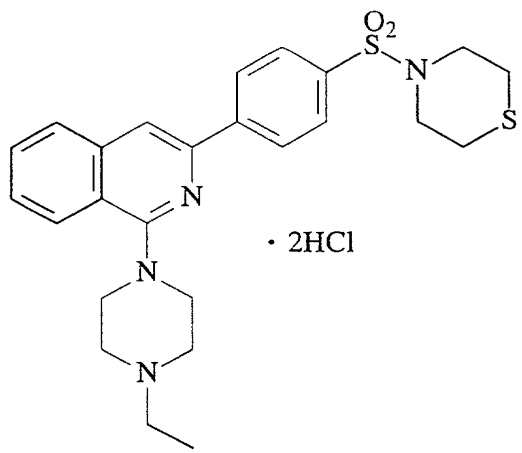
MS(FAB) m/z 467$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.57(q,J=7.2Hz,2H), 2.77(t,J=4.4Hz,4H), 3.06(t,J=4.8Hz,4H), 3.61(t,J=4.4Hz,4H), 3.76(t,J=4.8Hz,4H), 7.53(ddd,J=8.4,8.0,1.2Hz,1H), 7.64(ddd,J=8.4,8.0,1.2Hz,1H),

7.77(s,1H), 7.84(d,J=8.8Hz,2H), 7.85(d,J=8.0Hz,1H), 8.10(d,J=8.4Hz,1H), 8.34(d,J=8.8Hz,2H).

Example 76 Synthesis of 3-[(4-thiomorpholinyl)sulfonylphenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (550 mg, yield; 38%) from 4-(thiomorpholinylsulfonyl)bromobenzene (5.55 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (953 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 268-270°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 2.69(t,J=4.8Hz,4H), 3.18-3.20(m,6H), 3.32-3.40(m,2H), 3.55-3.64(m,4H), 4.03(d,J=13.6Hz,2H), 7.68(t,J=8.0Hz,1H), 7.80(t,J=8.0,Hz,1H), 7.88(d,J=8.8Hz,2H), 8.05(d,J=8.0Hz,1H),

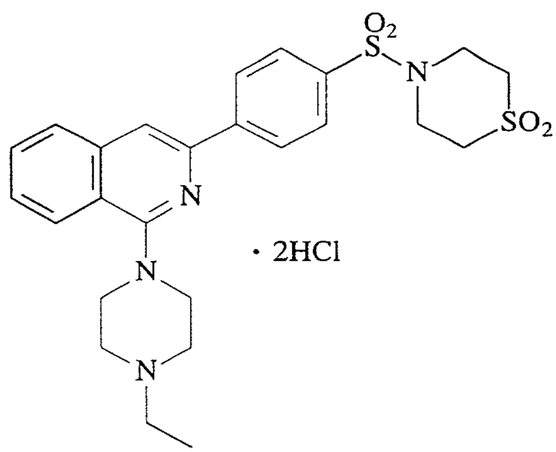
8.16(d,J=8.0Hz,1H), 8.28(s,1H), 8.46(d,J=8.8Hz,2H).

MS(FAB) m/z 483(M+H)$^+$

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.19(t,J=7.2Hz,3H), 2.58(q,J=7.2Hz,2H), 2.72-2.74(m,2H), 2.79(br,4H), 3.38-3.41(m,2H), 3.62(br,4H), 7.53(dt,J=8.0,1.2Hz,1H), 7.64(dt,J=8.0,1.2Hz,1H), 7.70(s,1H), 7.82(d,J=8.8Hz,2H), 7.83(d,J=8.0Hz,1H), 8.10(d,J=8.0Hz,1H), 8.32(d,J=8.8Hz,2H).

<u>Example 77 Synthesis of 3-[(1,1-dioxythiomorpholinyl)sulfonylphenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride</u>



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (673 mg, yield; 52%) from 1-bromo-4-(1,1-dioxythiomorpholinyl)sulfonylbenzene (3.59 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (811 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as

yellow crystals.

Hydrochloride:

m.p.; 198-200°C

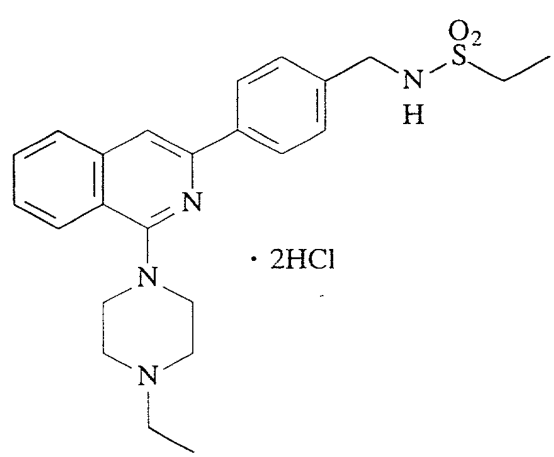
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 3.22-3.25(m,2H), 3.29-3.40(m,6H), 3.51-3.55(m,6H), 3.61(t,J=11.6Hz,2H), 4.04(d,J=13.6Hz,2H), 7.69(dt,J=8.0,1.2Hz,1H), 7.81(dt,J=8.0,1.2Hz,1H), 7.95(d,J=8.4Hz,2H), 8.05(d,J=8.0Hz,1H), 8.16(d,J=8.0Hz,1H), 8.30(s,1H), 8.49(d,J=8.4Hz,2H).

MS(FAB) m/z 515(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.10(br-t,3H), 2.66(br,2H), 3.29-3.31(m,4H), 3.34(br,4H), 3.49(br,8H), 7.64(t,J=8.0Hz,1H), 7.76(t,J=8.0Hz,1H), 7.94(d,J=8.8Hz,2H), 8.00(d,J=8.0Hz,1H), 8.10(d,J=8.0Hz,1H), 8.19(s,1H), 8.48(d,J=8.8Hz,2H).

<u>Example 78 Synthesis of 3-(4-ethylsulfonylaminomethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride</u>



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (655 mg, yield; 49%) from 1-bromo-4-ethylsulfonylaminobenzene (2.73 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (975 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

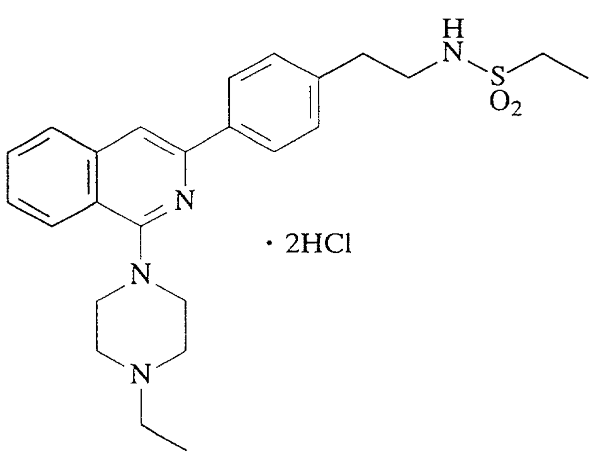
Hydrochloride:

MS(FAB) m/z 439$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.6Hz,3H), 1.35(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.77(br,4H), 3.00(q,J=7.6Hz,2H), 3.59(br,4H), 4.37(d,J=6.0Hz,2H), 4.59(br,1H), 7.45(d,J=8.4Hz,2H), 7.48(t,J=8.4Hz,1H), 7.60(t,J=8.4Hz,1H), 7.70(s,1H), 7.80(d,J=8.4Hz,1H), 8.09(d,J=8.4Hz,1H), 8.18(d,J=8.4Hz,2H).

Example 79 Synthesis of 3-(4-ethylsulfonylaminoethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (1.22 g, yield; 76%) from 1-bromo-4-ethylsulfonylaminoethylbenzene (3.54 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.14 g). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 194-197°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.16(t,J=7.2Hz,3H), 1.34(t,J=7.2Hz,3H), 2.84(t,J=7.2Hz,2H), 2.97(q,J=7.2Hz,2H), 3.19-3.24(m,4H), 3.33-3.39(m,2H), 3.56-3.63(m,4H), 4.00(d,J=13.2Hz,2H), 7.38(d,J=8.4Hz,2H), 7.61(dt,J=8.0,1.2Hz,1H), 7.75(dt,J=8.0,1.2Hz,1H), 7.99(d,J=8.0Hz,1H), 8.07(s,1H), 8.11(d,J=8.0Hz,1H), 8.13(d,J=8.4Hz,2H).

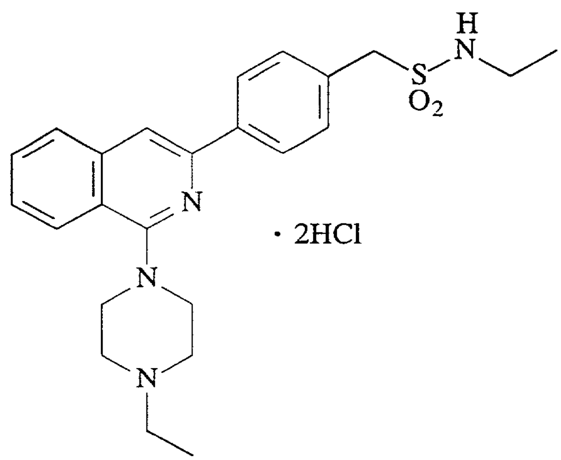
MS(FAB) m/z 453(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 1.28(t,J=7.6Hz,3H), 2.55(q,J=7.2Hz,2H), 2.76(br,4H), 2.92(t,J=6.4Hz,2H), 2.96(q,J=7.6Hz,2H), 3.41(t,J=6.4Hz,2H), 3.59(br,4H), 4.36(t,J=6.4Hz,1H), 7.30(d,J=8.4Hz,2H), 7.46(ddd,J=8.4,8.0,1.2Hz,1H), 7.58(ddd,J=8.4,8.0,1.2Hz,1H), 7.67(s,1H), 7.78(d,J=8.0Hz,1H), 8.07(d,J=8.4Hz,1H), 8.12(d,J=8.4Hz,2H).

Example 80 Synthesis of 3-(4-

ethylaminosulfonylmethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (449 mg, yield; 60%) from 1-bromo-4-ethylaminosulfonylmethylbenzene (1.28 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (550 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 154-156°C

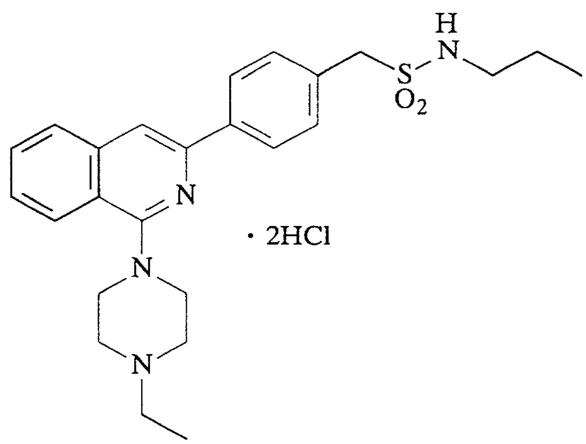
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.03(t,J=7.2Hz,3H), 1.31(t,J=7.2Hz,3H), 2.90-3.00(m,2H), 3.18-3.25(m,2H), 3.30-3.40(m,2H), 3.49-3.62(m,4H), 3.99(d,J=13.6Hz,2H), 4.37(s,2H), 7.09(br,1H), 7.48(d,J=8.4Hz,2H), 7.60(t,J=8.0Hz,1H), 7.74(t,J=8.0Hz,1H), 7.98(d,J=8.0Hz,1H), 8.10(s,1H), 8.11(d,J=8.0Hz,1H), 8.18(d,J=8.4Hz,2H).

MS(FAB) m/z 439$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.14-1.20(m,6H), 2.57(q,J=7.2Hz,2H), 2.78(br,4H), 3.10(dd,J=7.2,6.0Hz,2H), 3.60(br,4H), 4.07(t,J=6.0Hz,1H), 4.31(s,2H), 7.48(ddd,J=8.4,8.0,1.2Hz,1H), 7.49(d,J=8.4Hz,2H), 7.60(ddd,J=8.4,8.0,1.2Hz,1H), 7.71(s,1H), 7.80(d,J=8.0Hz,1H), 8.08(d,J=8.4Hz,1H), 8.19(d,J=8.4Hz,2H).

Example 81 Synthesis of 3-(4-propylaminosulfonylmethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (307 mg, yield; 28%) from 1-bromo-4-propylaminosulfonylmethylbenzene (1.62 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (766 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 194-197°C

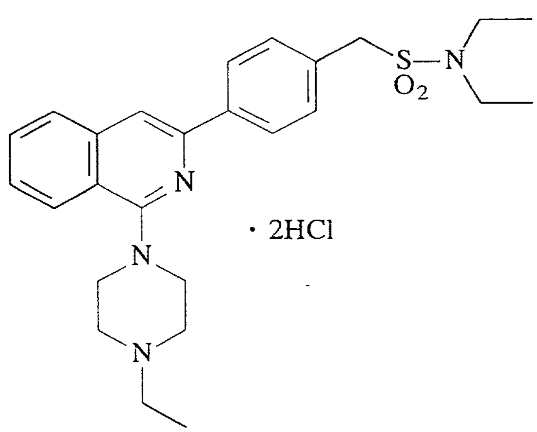
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.83(t,J=7.2Hz,3H), 1.31(t,J=7.2Hz,3H), 1.38-1.48(m,2H), 2.86-2.90(m,2H), 3.18-3.25(m,2H), 3.31-3.37(m,2H), 3.50-3.61(m,4H), 3.97-4.02(m,2H), 4.37(s,2H), 7.11(br,1H), 7.48(d,J=8.0Hz,2H), 7.60(t,J=8.0Hz,1H), 7.74(t,J=8.0Hz,1H), 7.98(d,J=8.0Hz,1H), 8.09(s,1H), 8.10(d,J=8.0Hz,1H), 8.18(d,J=8.0Hz,2H).

MS(FAB) m/z 453(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.91(t,J=7.2Hz,3H), 1.19(t,J=7.2Hz,3H), 1.54(q,J=7.2Hz,2H), 2.58(q,J=7.2Hz,2H), 2.79(br,4H), 3.02(q,J=7.2Hz,2H), 3.62(br,4H), 4.08(t,J=6.0Hz,1H), 4.32(s,2H), 7.48(ddd,J=8.4,8.0,1.2Hz,1H), 7.49(d,J=8.4Hz,2H), 7.61(ddd,J=8.4,8.0,1.2Hz,1H), 7.71(s,1H), 7.80(d,J=8.0Hz,1H), 8.08(d,J=8.4Hz,1H), 8.19(d,J=8.4Hz,2H).

Example 82 Synthesis of 3-[4-(N,N-diethylamino)sulfonylmethylphenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (101 mg, yield; 17%) from 1-bromo-4-N,N-diethylaminosulfonylmethylbenzene (819 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (530 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

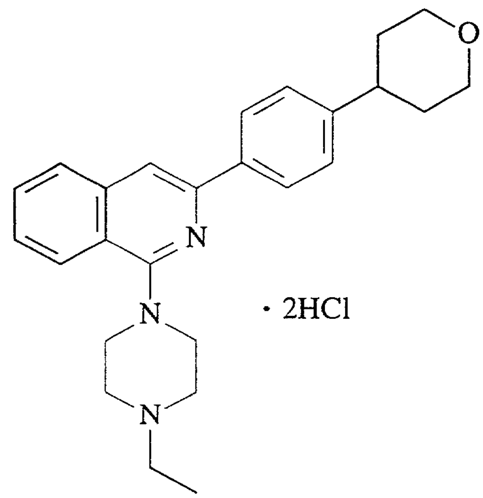
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.04(t,J=7.2Hz,6H), 1.31(t,J=7.2Hz,3H), 3.10(q,J=7.2Hz,4H), 3.18-3.25(m,2H), 3.30-3.38(m,2H), 3.51-3.61(m,4H), 4.00(d,J=13.2Hz,2H), 4.43(s,2H), 7.50(d,J=8.4Hz,2H), 7.60(t,J=8.0Hz,1H), 7.74(t,J=8.0Hz,1H), 7.98(d,J=8.0Hz,1H), 8.10(d,J=8.0Hz,1H), 8.11(s,1H), 8.20(d,J=8.4Hz,2H).

MS(FAB) m/z 467$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.12(t,J=7.2Hz,6H), 1.19(t,J=7.2Hz,3H), 2.58(q,J=7.2Hz,2H), 2.78(br,4H), 3.13(q,J=7.2Hz,4H), 3.61(br,4H), 4.27(s,2H), 7.46-7.50(m,1H), 7.48(d,J=8.0Hz,2H), 7.06(t,J=8.0Hz,1H), 7.72(s,1H), 7.80(d,J=8.0Hz,1H), 8.08(d,J=8.0Hz,1H), 8.19(d,J=8.0Hz,2H).

<u>Example 83 Synthesis of 3-[4-(tetrahydropyran-4-yl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride</u>



Methanol (80 ml) and platinum oxide (100 mg) were added to 3-[4-(5,6-dihydro-2H-pyran-4-yl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline (2.3 g), and the mixture was reacted at room temperature for 2 hr. The reaction solution was filtered through Celite, and then evaporated. The resulting residue was basified with a 1N aqueous solution of sodium hydroxide, and then partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and concentrated. Then, the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system), to give an oil (905 mg, yield; 47%). The oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 148-150°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 1.70-1.76(m,4H), 2.85(br,1H), 3.20-3.28(m,2H), 3.30-3.38(m,2H),

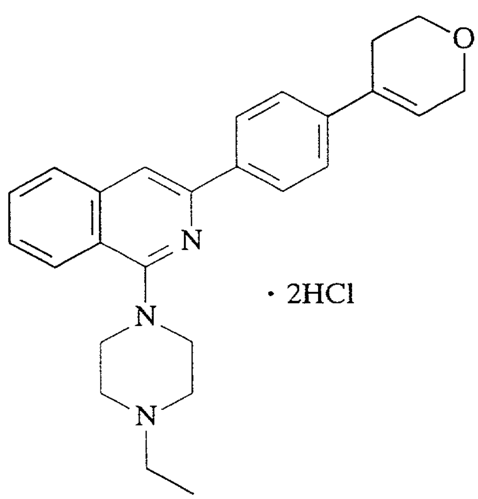
3.44-3.56(m,4H), 3.63(d,J=11.6Hz,2H), 3.95-4.01(m,4H), 7.40(d,J=8.4Hz,2H), 7.60(t,J=8.4Hz,1H), 7.74(t,J=8.4Hz,1H), 7.99(d,J=8.4Hz,1H), 8.06(s,1H), 8.11(d,J=8.4Hz,1H), 8.14(d,J=8.4Hz,2H).

MS(FAB) m/z 402$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.69-1.93(m,4H), 2.55(q,J=7.2Hz,2H), 2.76(br,4H), 2.75-2.88(m,1H), 3.53-3.59(m,2H), 3.59(br,4H), 4.09-4.13(m,2H), 7.33(d,J=8.4Hz,2H), 7.45(ddd,J=8.4,8.0,1.2Hz,1H), 7.58(ddd,J=8.4,8.0,1.2Hz,1H), 7.67(s,1H), 7.78(d,J=8.0Hz,1H), 8.07(d,J=8.4Hz,1H), 8.12(d,J=8.4Hz,2H).

Example 84 Synthesis of 3-[4-(5,6-dihydro-2H-pyran-4-yl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (443 mg, yield; 58%) from 1-bromo-(5,6-dihydro-2H-pyran-4-

yl)benzene (2.3 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (800 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 170-172°C

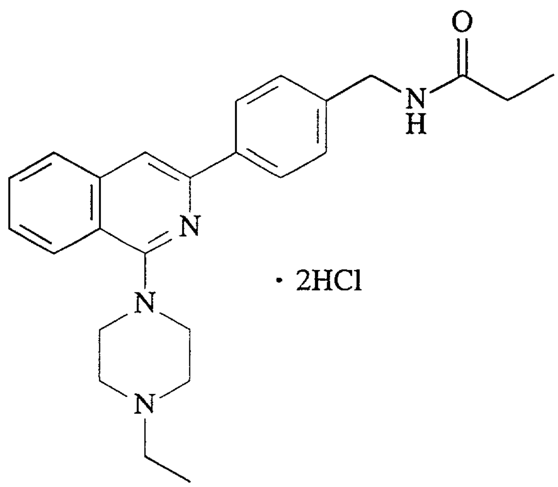
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 3.20-3.38(m,2H), 3.32-3.40(m,2H), 3.54(t,J=13.6Hz,4H), 3.63(d,J=12.0Hz,2H), 3.86(t,J=5.6Hz,2H), 4.01(d,J=14.0Hz,2H), 4.27(br,2H), 6.38(br,1H), 7.60(d,J=8.8Hz,2H), 7.61(t,J=8.0Hz,1H), 7.75(t,J=8.0Hz,1H), 7.99(d,J=8.0Hz,1H), 8.11(s,1H), 8.13(d,J=8.0Hz,1H), 8.20(d,J=8.8Hz,2H).

MS(FAB) m/z 400(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.52-2.58(m,2H), 2.54(q,J=7.2Hz,2H), 2.75(br,4H), 3.59(br,4H), 3.95(t,J=5.6Hz,2H), 4.35(t,J=2.8Hz,2H), 6.20(br,1H), 7.45(ddd,J=8.4,8.0,1.2Hz,1H), 7.48(d,J=8.8Hz,2H), 7.57(ddd,J=8.4,8.0,1.2Hz,1H), 7.68(s,1H), 7.77(d,J=8.0Hz,1H), 8.07(d,J=8.0Hz,1H), 8.14(d,J=8.8Hz,2H).

Example 85 Synthesis of 3-(4-ethylcarbonylaminomethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (608 mg, yield; 59%) from 1-bromo-4-ethylcarbonylaminomethylbenzene (2.31 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (808 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

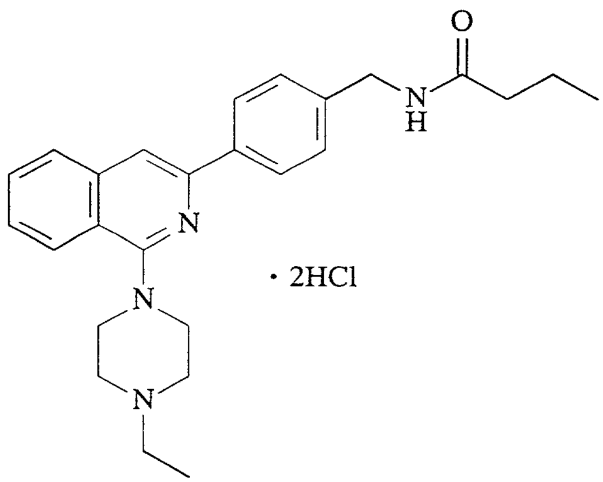
Hydrochloride:

m.p.; 171-174°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.05(t,J=7.6Hz,3H), 1.33(t,J=7.2Hz,3H), 2.17(q,J=7.6Hz,2H), 3.15-3.28(m,2H), 3.30-3.38(m,2H), 3.53(t,J=12.8Hz,2H), 3.61(d,J=11.2Hz,2H), 3.99(d,J=12.8Hz,2H), 4.32(d,J=6.0Hz,2H), 7.38(d,J=8.4Hz,2H), 7.61(t,J=8.0Hz,1H), 7.74(t,J=8.0Hz,1H), 7.99(d,J=8.0Hz,1H), 8.07(s,1H), 8.11(d,J=8.0Hz,1H), 8.15(d,J=8.4Hz,2H), 8.37(t,J=6.0Hz,1H).

MS(FAB) m/z 403(M+H)$^+$.

Example 86 Synthesis of 3-(4-propylcarbonylaminomethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (777 mg, yield; 52%) from 1-bromo-4-propylcarbonylaminomethylbenzene (2.34 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.14 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 126-128°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.88(t,J=7.2Hz,3H), 1.33(t,J=7.2Hz,3H), 1.57(q,J=7.2Hz,2H), 2.15(t,J=7.2Hz,2H), 3.18-3.26(m,2H), 3.30-3.40(m,2H), 3.52-3.63(m,4H), 4.00(d,J=13.6Hz,2H), 4.33(d,J=6.0Hz,2H), 7.38(d,J=8.4Hz,2H), 7.61(t,J=8.0Hz,1H), 7.74(t,J=8.0Hz,1H), 7.98(d,J=8.0Hz,1H),

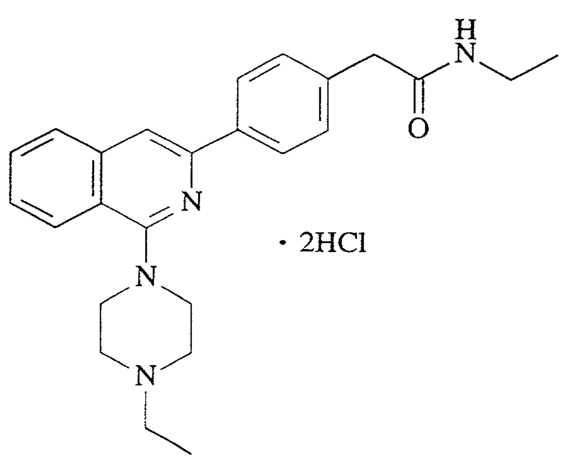
8.07(s,1H), 8.11(d,J=8.0Hz,1H), 8.12(d,J=8.4Hz,2H), 8.40(t,J=6.0Hz,1H).

MS(FAB) m/z 417(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.98(t,J=7.2Hz,3H), 1.18(t,J=7.2Hz,3H), 1.67-1.76(m,2H), 2.22(t,J=7.2Hz,2H), 2.55(q,J=7.2Hz,2H), 2.76(br,4H), 3.59(br,4H), 4.50(d,J=5.6Hz,2H), 5.75(br,1H), 7.37(d,J=8.4Hz,2H), 7.46(t,J=8.0Hz,1H), 7.59(t,J=8.0Hz,1H), 7.68(s,1H), 7.79(d,J=8.0Hz,1H), 8.08(d,J=8.0Hz,1H), 8.14(d,J=8.4Hz,2H).

Example 87 Synthesis of 3-(4-ethylaminocarbonylmethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (587 mg, yield; 56%) from 1-bromo-4-ethylaminocarbonylmethylbenzene (1.29 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (830 mg). The free compound

was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 143-145°C

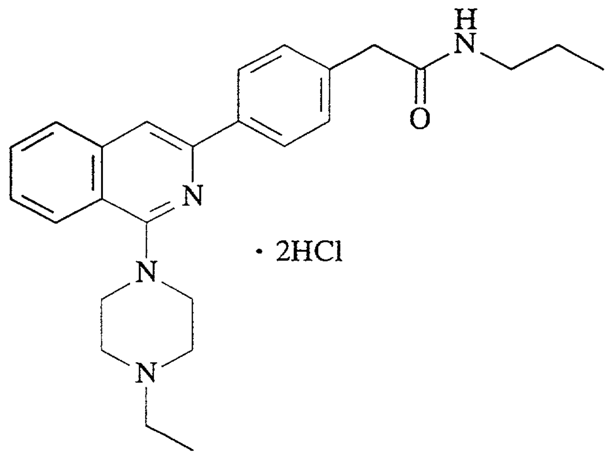
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.03(t,J=7.2Hz,3H), 1.33(t,J=7.2Hz,3H), 3.06-3.12(m,2H), 3.18-3.26(m,2H), 3.30-3.38(m,2H), 3.46(s,2H), 3.52-3.63(m,4H), 4.00(d,J=13.2Hz,2H), 7.39(d,J=8.4Hz,2H), 7.60(dt,J=8.0,1.2Hz,1H), 7.74(dt,J=8.0,1.2Hz,1H), 7.98(d,J=8.0Hz,1H), 8.07(s,1H), 8.11(d,J=8.0Hz,1H), 8.12(d,J=8.4Hz,2H).

MS(FAB) m/z 403$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.61(t,J=7.2Hz,3H), 1.18(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.78(br,4H), 3.23-3.29(m,2H), 3.60(br,4H), 3.64(s,2H), 5.40(br,1H), 7.35(d,J=8.4Hz,2H), 7.45(t,J=8.0Hz,1H), 7.60(t,J=8.0Hz,1H), 7.70(s,1H), 7.80(d,J=8.0Hz,1H), 8.09(d,J=8.0Hz,1H), 8.17(d,J=8.4Hz,2H).

Example 88 Synthesis of 3-(4-propylaminocarbonylmethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (517 mg, yield; 56%) from 1-bromo-4-propylaminocarbonylmethylbenzene (2.01 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (706 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 138-141°C

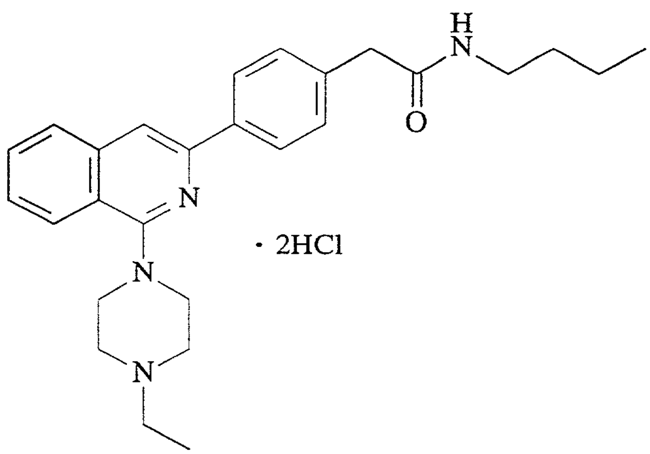
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.84(t,J=7.2Hz,3H), 1.33(t,J=7.2Hz,3H), 1.40-1.45(m,2H), 3.03(q,J=7.2Hz,2H), 3.22(t,J=7.2Hz,2H), 3.30-3.40(m,2H), 3.47(s,2H), 3.52-3.63(m,4H), 4.01(d,J=13.2Hz,2H), 7.39(d,J=8.0Hz,2H), 7.61(t,J=8.0Hz,1H), 7.74(t,J=8.0Hz,1H), 7.98(d,J=8.0Hz,1H), 8.07(s,1H), 8.11(d,J=8.0Hz,1H), 8.12(d,J=8.0Hz,2H).

MS(FAB) m/z 417(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz, $CDCl_3$); δ (ppm) 0.84(t,J=7.2Hz,3H), 1.18(t,J=7.2Hz,3H), 1.40-1.50(m,2H), 2.56(q,J=7.2Hz,2H), 2.77(br,4H), 3.18(q,J=6.4Hz,2H), 3.59(br,4H), 3.65(s,2H), 5.42(br,1H), 7.36(d,J=8.4Hz,2H), 7.48(t,J=8.0Hz,1H), 7.60(t,J=8.0Hz,1H), 7.70(s,1H), 7.80(d,J=8.0Hz,1H), 8.09(d,J=8.0Hz,1H), 8.17(d,J=8.4Hz,2H).

Example 89 Synthesis of 3-(4-butylaminocarbonylmethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (615 mg, yield; 67%) from 1-bromo-4-butylaminocarbonylmethylbenzene (1.75 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (679 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 133-136°C

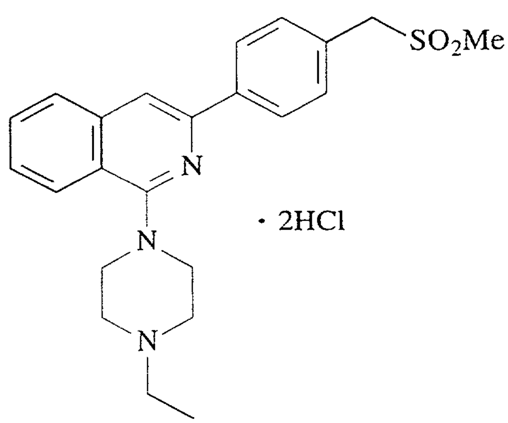
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.87(t,J=7.2Hz,3H), 1.27-1.42(m,7H), 3.06(q,J=6.4Hz,2H), 3.18-3.26(m,2H), 3.30-3.38(m,2H), 3.47(s,2H), 3.51-3.63(m,4H), 4.00(d,J=13.6Hz,2H), 7.39(d,J=8.4Hz,2H), 7.61(t,J=8.0Hz,1H), 7.74(t,J=8.0Hz,1H), 7.95(d,J=8.0Hz,1H), 8.06(s,1H), 8.11(d,J=8.0Hz,1H), 8.12(d,J=8.4Hz,2H).

MS(FAB) m/z 431(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.88(t,J=7.2Hz,3H), 1.18(t,J=7.2Hz,3H), 1.32-1.42(m,2H), 1.37-1.44(m,2H), 2.56(q,J=7.2Hz,2H), 2.76(br,4H), 3.21(q,J=6.4Hz,2H), 3.59(br,4H), 3.64(s,2H), 5.39(br,1H), 7.35(d,J=8.4Hz,2H), 7.48(t,J=8.0Hz,1H), 7.60(t,J=8.0Hz,1H), 7.71(s,1H), 7.80(d,J=8.0Hz,1H), 8.09(d,J=8.0Hz,1H), 8.17(d,J=8.4Hz,2H).

Example 90 Synthesis of 3-(4-methylsulfonylmethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (430

mg, yield; 49%) from 1-bromo-4-methylsulfonylmethylbenzene (1.26 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (685 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 260-262°C

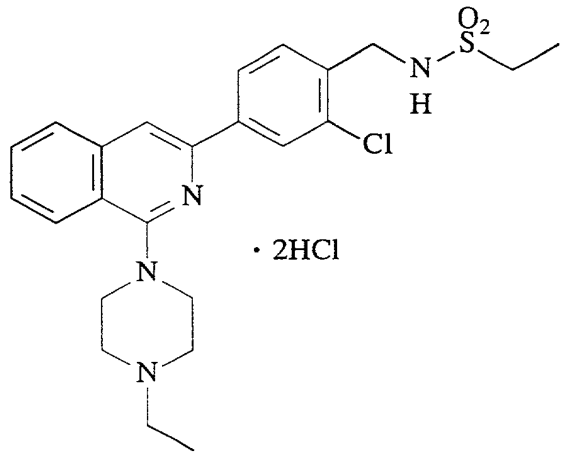
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 2.95(s,3H), 3.18-3.28(m,2H), 3.30-3.38(m,2H), 3.55-3.63(m,4H), 4.02(d,J=13.6Hz,2H), 4.57(s,2H), 7.55(d,J=8.4Hz,2H), 7.63(t,J=8.0Hz,1H), 7.76(t,J=8.0Hz,1H), 8.00(d,J=8.0Hz,1H), 8.13(d,J=8.0Hz,1H), 8.13(s,1H), 8.23(d,J=8.4Hz,2H).

MS(FAB) m/z 410$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.77(br,4H), 2.79(s,2H), 3.59(br,4H), 4.32(s,2H), 7.49(ddd,J=8.4,8.0,1.2Hz,1H), 7.51(d,J=8.4Hz,2H), 7.61(ddd,J=8.4,8.0,1.2Hz,1H), 7.72(s,1H), 7.81(d,J=8.0Hz,1H), 8.09(d,J=8.4Hz,1H), 8.22(d,J=8.0Hz,2H).

<u>Example 91 Synthesis of 3-(3-chloro-4-ethylsulfonylaminomethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride</u>



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (101 mg, yield; 17%) from 3-chloro-4-ethylsulfonylaminomethyl-bromobenzene (819 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (530 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 278-280°C (decomp.)

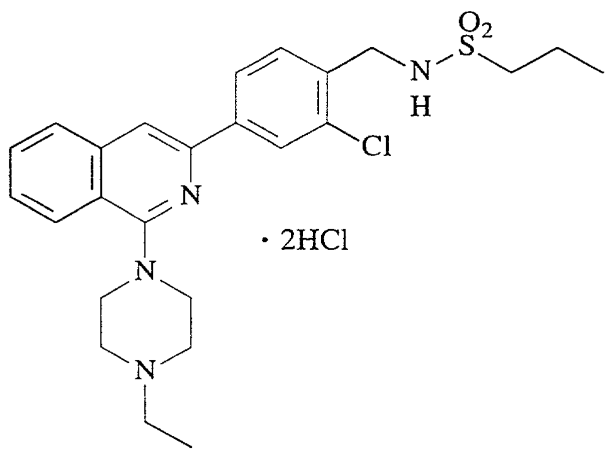
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.20(t,J=7.2Hz,3H), 1.31(t,J=7.2Hz,3H), 3.04(q,J=7.2Hz,2H), 3.18-3.25(m,2H), 3.28-3.37(m,2H), 3.51(t,J=12.8Hz,2H), 3.62(d,J=11.6Hz,2H), 3.97-4.03(m,2H), 4.29(d,J=6.0Hz,2H), 7.62(t,J=8.0Hz,1H), 7.66(d,J=8.0Hz,1H), 7.75(t,J=8.0Hz,1H), 7.99(d,J=8.0Hz,1H), 8.12(d,J=8.0Hz,1H), 8.18(dd,J=8.0,1.6Hz,1H), 8.18(s,1H), 8.24(d,J=1.6Hz,1H).

MS(FAB) m/z 473$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz, $CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.30(t,J=7.6Hz,3H), 2.56(q,J=7.2Hz,2H), 2.77(br,4H), 2.93(q,J=7.6Hz,2H), 3.59(br,4H), 4.45(d,J=6.4Hz,2H), 4.88(br,1H), 7.50(ddd,J=8.4,8.0,1.2Hz,1H), 7.52(d,J=8.0Hz,1H), 7.61(ddd,J=8.4,8.0,1.2Hz,1H), 7.68(s,1H), 7.80(d,J=8.4Hz,1H), 8.05(dd,J=8.0,1.6Hz,1H), 8.08(d,J=8.4Hz,1H), 8.23(d,J=1.6Hz,1H).

Example 92 Synthesis of 3-(3-chloro-4-propylsulfonylaminomethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (365 mg, yield; 39%) from 3-chloro-4-propylsulfonylaminomethyl-bromobenzene (1.58 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (825 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 253-255°C (decomp.)

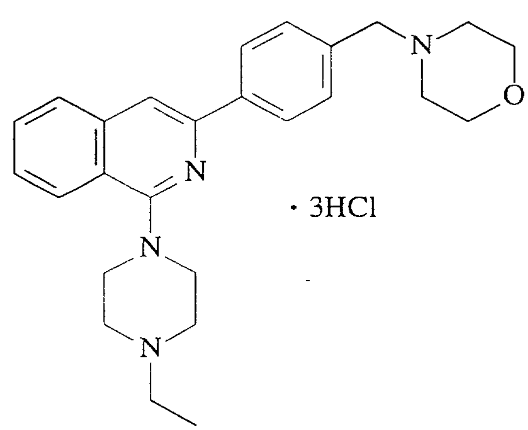
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.94(t,J=7.6Hz,3H), 1.31(t,J=7.2Hz,3H), 1.62-1.74(m,2H), 2.98-3.02(m,2H), 3.18-3.25(m,2H), 3.30-3.38(m,2H), 3.50(t,J=12.8Hz,2H), 3.62(d,J=11.6Hz,2H), 3.99(d,J=13.2Hz,2H), 4.28(d,J=6.0Hz,2H), 7.62(t,J=8.0Hz,1H), 7.65(d,J=8.0Hz,1H), 7.75(t,J=8.0Hz,1H), 7.99(d,J=8.0Hz,1H), 8.12(d,J=8.0Hz,1H), 8.18(dd,J=8.0,2.0Hz,1H), 8.18(s,1H), 8.24(d,J=2.0Hz,1H).

MS(FAB) m/z 488$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.96(t,J=7.6Hz,3H), 1.19(t,J=7.2Hz,3H), 1.76-1.81(m,2H), 2.57(q,J=7.2Hz,2H), 2.77(br,4H), 2.87-2.91(m,2H), 3.59(br,4H), 4.45(d,J=6.4Hz,2H), 4.82(t,J=6.4Hz,1H), 7.50(t,J=8.4Hz,1H), 7.52(d,J=8.0Hz,1H), 7.61(t,J=8.4Hz,1H), 7.68(s,1H), 7.80(d,J=8.4Hz,1H), 8.05(dd,J=8.0,1.6Hz,1H), 8.08(d,J=8.4Hz,1H), 8.23(d,J=1.6Hz,1H).

Example 93 Synthesis of 3-(4-morpholinylmethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (472 mg, yield; 71%) from 4-morpholinylmethyl-bromobenzene (1.02 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (651 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as a yellow amorphous.

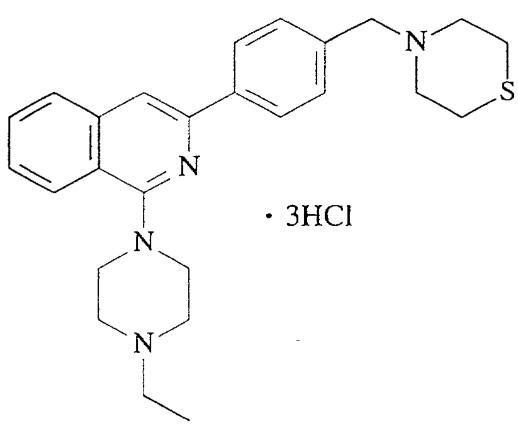
Hydrochloride (amorphous):

MS(FAB) m/z 417$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.49(t,J=4.8Hz,4H), 2.54(q,J=7.2Hz,2H), 2.77(br,4H), 3.56(s,2H), 3.60(br,4H), 3.73(t,J=4.8Hz,4H), 7.42(d,J=8.4Hz,2H), 7.46(dt,J=8.0,1.2Hz,1H), 7.59(dt,J=8.0,1.2Hz,1H), 7.69(s,1H), 7.79(d,J=8.0Hz,1H), 8.08(d,J=8.0Hz,1H), 8.12(d,J=8.4Hz,2H).

Example 94 Synthesis of 3-(4-thiomorpholinylmethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and

20, the free compound of the title compound was obtained (273 mg, 22%) from 4-thiomorpholinylmethyl-bromobenzene (1.08 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (882 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 193-197°C

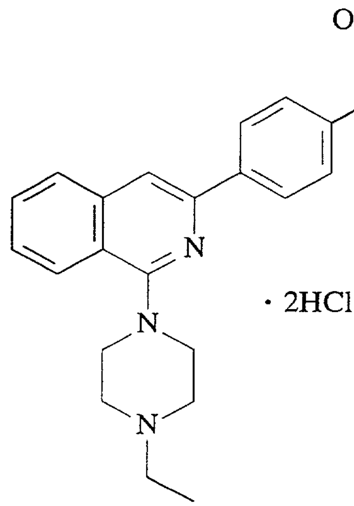
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 2.81(d,J=14.4Hz,2H), 3.08-3.16(m,2H), 3.21-3.38(m,6H), 3.53-3.65(m,6H), 4.01(d,J=12.8Hz,2H), 4.40(d,J=5.2Hz,2H), 7.64(t,J=8.0Hz,1H), 7.77(t,J=8.0Hz,1H), 7.79(d,J=8.4Hz,2H), 8.01(d,J=8.0Hz,1H), 8.14(d,J=8.0Hz,1H), 8.17(s,1H), 8.28(d,J=8.4Hz,2H).

MS(FAB) m/z 433$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.56(t,J=7.2Hz,4H), 2.68-2.77(m,10H), 3.58(s,2H), 3.68(br,4H), 7.40(d,J=8.0Hz,2H), 7.46(ddd,J=8.4,8.0,1.2Hz,1H), 7.59(ddd,J=8.4,8.0,1.2Hz,1H), 7.69(s,1H), 7.79(d,J=8.0Hz,1H), 8.07(d,J=8.4Hz,1H), 8.12(d,J=8.0Hz,2H).

Example 95 Synthesis of 3-[4-(3-oxazolidinone)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (1.0 g, yield; 71%) was obtained from 1-bromo-4-(3-oxazolidinone)benzene (2.29 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.19 g). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 171-174°C

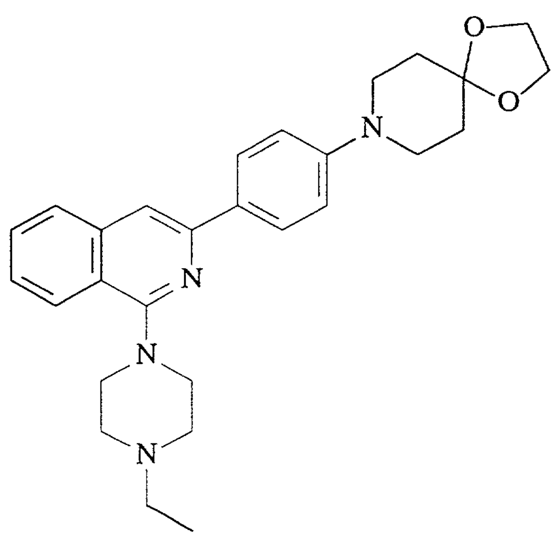
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 3.20-3.28(m,2H), 3.32-3.39(m,2H), 3.54(t,J=12.8Hz,2H), 3.62(d,J=10.8Hz,2H), 4.02(d,J=13.6Hz,2H), 4.14(t,J=8.0Hz,2H), 4.46-4.50(m,2H), 7.60(t,J=8.0Hz,1H), 7.71(d,J=8.8,Hz,2H), 7.74(t,J=8.0Hz,1H), 7.98(d,J=8.0Hz,1H), 8.08(s,1H), 8.11(d,J=8.0Hz,1H), 8.24(d,J=8.8Hz,2H).

MS(FAB) m/z 403(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz, $CDCl_3$); δ (ppm) 1.19(t, J=7.2Hz, 3H), 2.58(q, J=7.2Hz, 2H), 2.79(br, 4H), 3.61(br, 4H), 4.04-4.08(m, 2H), 4.44-4.48(m, 2H), 7.44(ddd, J=8.4, 8.0, 1.2Hz, 1H), 7.57(ddd, J=8.4, 8.0, 1.2Hz, 1H), 7.61(d, J=8.8Hz, 2H), 7.65(s, 1H), 7.76(d, J=8.0Hz, 1H), 8.04(d, J=8.0Hz, 1H), 8.16(d, J=8.8Hz, 2H).

Example 96 Synthesis of 3-[4-(4,4-ethylenedioxypiperidin-1-yl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline



3-Bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.72 g) and 4-(4,4-ethylenedioxypiperidin-1-yl)phenyltributylstannum (3.12 g) were reacted in the presence of tetrakistriphenylphosphine dichloride (0.5 g) in xylene (50 ml) at 140°C for 5 hr. The reaction solution was concentrated, and ethyl acetate and an aqueous saturated solution of sodium bicarbonate were added to the resulting residue, for partitioning. The resulting organic layer was washed with water and brine, dried over magnesium sulfate and evaporated. The resulting residue was purified by silica gel column

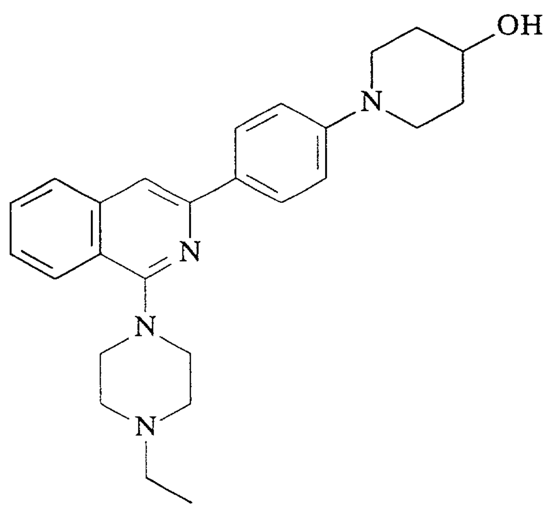
chromatography (methylene chloride/methanol system), to give 1.27 g of the title compound as a white powder.

Free compound:

m.p.; 118°C

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.87(br-t,4H), 2.55(q,J=7.2Hz,2H), 2.75(br-s,4H), 3.42(m,4H), 3.58(br-s,4H), 4.01(s,4H), 7.03(d,J=8.8Hz,2H), 7.41(br-t,1H), 7.55(br-t,1H), 7.60(s,1H), 7.75(d,J=8.0Hz,1H), 8.05(d,J=8.0Hz,1H), 8.08(dd,J=8.8Hz,2H).

<u>Example 97</u> <u>Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(4-hydroxypiperidin-1-yl)phenyl]isoquinoline trihydrochloride</u>



3-[4-(4,4-Ethylenedioxypiperidin-1-yl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline (290 mg) obtained in Example 96 was treated with camphorsulfonic acid and methanol. Then, a 2N aqueous solution of hydrochloric acid (50 ml) was added thereto, and the mixture was reacted for 1 hr. The reaction solution was basified and extracted with ethyl acetate. The resulting organic layer was washed with water and brine, and

dried over magnesium sulfate. The solvent was evaporated, the resulting residue was dissolved in methanol (20 ml), and then it was reacted with sodium borohydride (54 mg). The reaction solution was evaporated, and the reuslting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 119 mg of the free compound of the title compound as a white solid.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.71(m,2H), 2.04(m,2H), 2.55(q,J=7.2Hz,2H), 2.76(br-s,4H), 3.00(ddd,J=12.8,10.0,3.0Hz,2H), 3.56(br-s,4H), 3.67(dt,J=12.8,4.4Hz,2H), 3.88(m,1H), 7.02(d,J=8.8Hz,2H), 7.41(br-t,1H), 7.55(br-t,1H), 7.60(s,1H), 7.75(d,J=8.0Hz,1H), 8.05(d,J=8.0Hz,1H), 8.08(d,J=8.8Hz,2H).

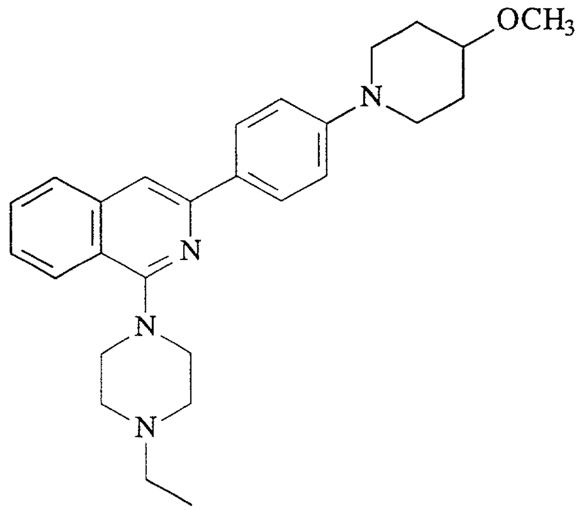
The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 148 mg of the title compound as a white powder.

Hydrochloride:

m.p.; 178°C

MS(FAB) m/z 417$(M+H)^+$.

Example 98 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(4-methoxypiperidin-1-yl)phenyl]isoquinoline trihydrochloride



3-Bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.79 g) and 4-(4-methoxypiperidin-1-yl)phenyltributylstannum (1.30 g) were reacted in the presence of tetrakistriphenylphosphine dichloride (0.30 g) in xylene (30 ml) at 140°C for 5 hr. The reaction solution was concentrated, and ethyl acetate and an aqueous solution of saturated sodium bicarbonate were added to the resulting residue, for partitioning. The resulting organic layer was washed with water and brine, dried over magnesium sulfate, and the solvent was evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.17 g of the free compound of the title compound as a yellow solid.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.72(m,2H), 2.03(m,2H), 2.55(q,J=7.2Hz,2H), 2.76(br-s,4H), 3.00(ddd,J=12.8,10.0,3.0Hz,2H), 0.40(s,3H), 3.48(m,1H), 3.59(br-s,4H), 7.02(d,J=8.8Hz,2H), 7.41(br-t,1H), 7.55(br-

t,1H), 7.61(s,1H), 7.75(d,J=8.0Hz,1H), 8.05(d,J=8.0Hz,1H), 8.08(d,J=8.8Hz,2H).

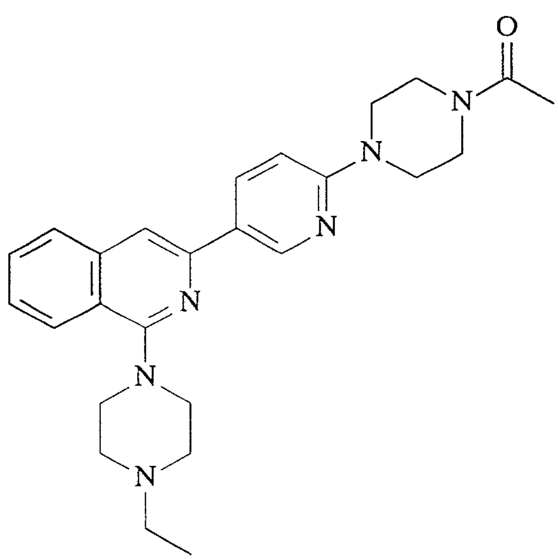
The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 0.24 g of the title compound as a yellow powder.

Hydrochloride:

m.p.; 165°C

MS(FAB) m/z 431(M+H)$^+$.

Example 99 Synthesis of 3-[2-(4-acetylpiperazin-1-yl)pyridin-5-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline trihydrochloride



3-Bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.53 g) and [2-(4-acetylpiperazin-1-yl)pyridin-5-yl]tributylstannum (0.91 g) were reacted in the presence of tetrakistriphenylphosphine dichloride (0.30 g) in xylene (30 ml) at 140°C for 5 hr. The reaction solution was concentrated.

Ethyl acetate and an aqueous solution of saturated sodium bicarbonate were added to the resulting residue, for partitioning. The resulting organic layer was washed with water and brine, dried over magnesium sulfate, and the solvent was evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.67 g of the free compound of the tilte compound as a white powder.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.21(t,J=7.2Hz,3H), 2.16(s,3H), 2.81(br-s,4H), 3.56-3.66(m,8H), 3.73(m,2H), 3.78(m,2H), 6.75(d,J=8.8Hz,2H), 7.44(br-t,1H), 7.56(s,1H), 7.57(br-t,1H), 7.76(d,J=8.0Hz,1H), 8.04(d,J=8.0Hz,1H), 8.28(dd,J=8.8,2.4Hz,1H), 9.01(d,J=2.4Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 0.72 g of the title compound as a yellow powder.

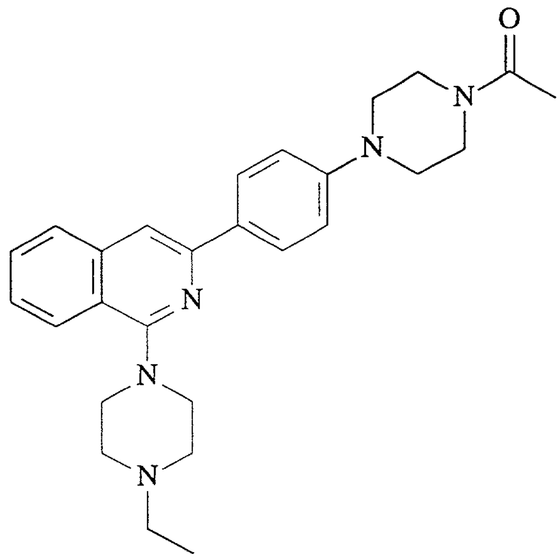
Hydrochloride:

m.p.; 206°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 2.08(s,3H), 3.23(m,2H), 3.37(m,2H), 3.54(br-t,2H), 3.61-3.69(m,6H), 3.77(br,2H), 3.86(br,2H), 3.98(br-d,2H), 7.42(m,1H), 7.63(br-t,1H), 7.77(br-t,1H), 7.97(br-d,1H), 8.11-8.16(m,2H), 8.65(m,1H), 8.79(br,1H).

Example 100 Synthesis of 3-[4-(4-acetylpiperazin-1-

yl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline trihydrochloride



3-Bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.27 g) and [4-(4-acetylpiperidin-1-yl)phenyl]tributylstannum (0.90 g) were reacted in the presence of tetrakistriphenylphosphine dichloride (0.30 g) in xylene (30 ml) at 140°C for 5 hr. The reaction solution was concentrated. Ethyl acetate and an aqueous solution of saturated sodium bicarbonate were added to the resulting residue, for partitioning. The resulting organic layer was washed with water and brine, dried over magnesium sulfate, and the solvent was evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.12 g of the free compound of the title compound as a white solid.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.21(t,J=7.2Hz,3H), 2.16(s,3H),

2.60(q,J=7.2Hz,2H), 2.81(br-s,4H), 3.26(m,4H), 3.62(br-s,4H), 3.65(m,2H), 3.81(m,2H), 7.02(d,J=8.8Hz,2H), 7.43(br-t,1H), 7.58(br-t,1H), 7.62(s,1H), 7.77(d,J=8.4Hz,1H), 8.05(d,J=8.4Hz,1H), 8.11(d,J=8.88Hz,2H).

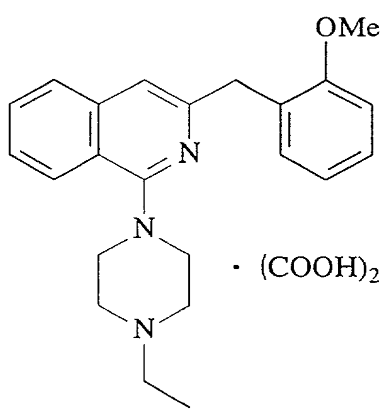
The resulting free compound form was converted into a hydrochloride in a conventional manner, recrystallized from ethanol/ether, to give 0.16 g of the title compound as a yellow powder.

Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 2.07(s,3H), 3.22-3.28(m,4H), 3.51(br-t,2H), 3.60-3.68(m,4H), 3.98(br-d,2H), 7.17(m,1H), 7.56(br-t,1H), 7.71(br-t,1H), 7.94(br-d,1H), 7.94(br-d,1H), 7.98(br-s,1H), 8.07-8.13(m,2H).

MS(FAB) m/z 431 $(M+H)^+$.

Example 101 Synthesis of 3-(2-methoxybenzyl)-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



Potassium hydroxide (117 mg) and hydrazine monohydrate (2 ml) were added to a solution of 3-(2-methoxyphenylcarbonyl)-1-(4-ethylpiperazin-1-

yl)isoquinoline (261 mg) in ethylene glycol (6 ml), and the resulting mixture was reacted at 140°C overnight. Water and ethyl acetate were added to the reaction solution, for partitioning. The resulting organic layer was washed with brine, dried and evaporated. The resulting residue was then purified by NH-silica gel column chromatography (ethyl acetate/hexane system), to give a yellow oil (185 mg, yield; 73%). The resulting oil was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 194-197°C

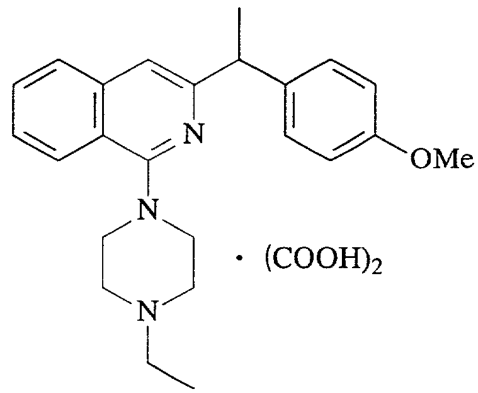
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.25(br,3H), 3.14(br,2H), 3.35(br,4H), 3.60(br,4H), 3.78(s,3H), 4.08(s,2H), 6.89(br,1H), 7.00(d,J=8.0Hz,1H), 7.09(s,1H), 7.17(d,J=8.0Hz,1H), 7.23(br,1H), 7.54(br,1H), 7.66(br,1H), 7.78(d,J=8.0Hz,1H), 8.05(d,J=8.0Hz,1H).

MS(FAB) m/z 374(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 2.53(q,J=7.2Hz,2H), 2.70(br,4H), 3.47(br,4H), 3.82(s,3H), 4.16(s,2H), 6.87-6.91(m,2H), 6.94(s,1H), 7.19-7.24(m,2H), 7.38(dt,J=8.0,0.8Hz,1H), 7.49(dt,J=8.0,0.8Hz,1H), 7.60(d,J=8.0Hz,1H), 8.01(d,J=8.0Hz,1H).

Example 102 Synthesis of 3-[α-methyl-(4-methoxybenzyl)]-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



3-[1-(4-Methoxyphenyl)ethen-1-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline obtained in Example 217 was converted into the hydrochloride. To the hydrochloride (145 mg) were added methanol (15 ml) and palladium/carbon catalyst (10 mg), and the resulting mixture was reacted in hydrogen atmosphere at room temperature overnight. The reaction solution was filtered through Celite, and then evaporated. The resulting residue was basified by adding a 1N aqueous solution of sodium hydroxide thereto, which was then extracted with ethyl acetate. The resulting organic layer was washed with brine, dried and evaporated. Then, the residue was purified by NH-silica gel column chromatography (ethyl acetate/hexane system), to give a yellow oil (140 mg, yield; 96%). The oil was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 86-88°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.25(t,J=7.2Hz,3H), 1.64(d,J=6.8Hz,3H), 3.13(br,2H), 3.35(br,4H), 3.60(br,4H),

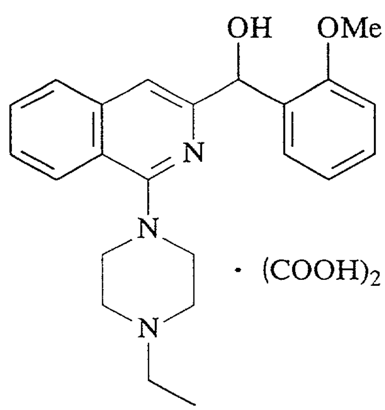
3.70(s,3H), 4.22(q,J=6.8Hz,1H), 6.84(d,J=8.4Hz,2H), 7.29(s,1H), 7.30(d,J=8.4Hz,2H), 7.54(t,J=8.0Hz,1H), 7.67(t,J=8.0Hz,1H), 7.82(d,J=8.0Hz,1H), 8.04(t,J=8.0Hz,1H).

MS(FAB) m/z 376(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.6Hz,3H), 1.70(d,J=7.2Hz,3H), 2.54(q,J=7.6Hz,2H), 2.71(br,4H), 3.48(br,4H), 3.77(s,3H), 4.18(q,J=7.2Hz,1H), 6.82(d,J=8.8Hz,2H), 7.00(s,1H), 7.36(d,J=8.8Hz,2H), 7.39(ddd,J=8.4,8.0,1.2Hz,1H), 7.50(ddd,J=8.4,8.0,1.2Hz,1H), 7.62(d,J=8.0Hz,1H), 8.00(d,J=8.4Hz,1H).

Example 103 Synthesis of 3-[α-hydroxy-(2-methoxybenzyl)]-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



In the same manner as in Example 104, the free compound of the title compound was obtained (1.13 g, yield; 91%) from o-anisaldehyde (0.8 ml) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.05 g). The resulting free compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 100-103°C

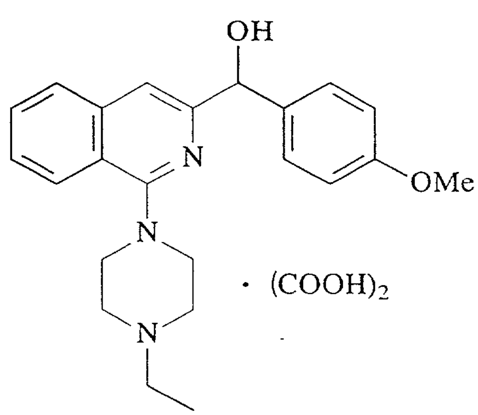
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.20(t,J=7.2Hz,3H), 3.00(br,2H), 3.20(br,4H), 3.56(br,4H), 3.60(br,1H), 3.78(s,3H), 6.09(s,1H), 6.89(t,J=7.2Hz,1H), 6.97(d,J=7.2Hz,1H), 7.21(dt,J=7.6,2.0Hz,1H), 7.33(dd,J=7.6,2.0Hz,1H), 7.47(s,1H), 7.55(t,J=8.0Hz,1H), 7.68(t,J=8.0Hz,1H), 7.90(d,J=8.0Hz,1H), 8.03(d,J=8.0Hz,1H).

MS(FAB) m/z 378$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.73(br,4H), 3.54(br,4H), 3.89(s,3H), 5.24(d,J=5.6Hz,1H), 6.23(d,J=5.6Hz,1H), 6.89-6.94(m,2H), 7.14(s,1H), 7.23(dt,J=7.2,1.6Hz,1H), 7.40(dd,J=7.2,1.6Hz,1H), 7.43(ddd,J=8.4,8.0,1.2Hz,1H), 7.54(ddd,J=8.4,8.0,1.2Hz,1H), 7.64(d,J=8.0Hz,1H), 8.04(d,J=8.0Hz,1H).

Example 104 Synthesis of 3-[α-Hydroxy-(4-methoxybenzyl)]-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



To a solution of 3-bromo-1-(4-ethylpiperazin-1-

yl)isoquinoline (1.08 g) in tetrahydrofuran (20 ml) was added 1.7 M t-butyl lithium (3.0 ml) at -78 °C, and the mixture was stirred for 15 min. Thereafter, p-anisaldehyde (0.82 ml) was added at -78 °C, and the mixture was stirred for 15 min. The reaction solution was poured into an aqueous solution of saturated ammonium chloride, and then extracted with ethyl acetate. The resulting organic layer was washed with water and brine, dried and evaporated. Then, the residue was purified by NH-silica gel column chromatography (ethyl acetate/hexane system), to give a yellow oil (1.23 g, yield; 97%). The oil was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 95-97°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.21(t,J=7.2Hz,3H), 3.02(br,2H), 3.23(br,4H), 3.46(br,4H), 3.60(t,J=6.8Hz,1H), 3.70(s,3H), 5.69(s,1H), 6.84(d,J=8.8Hz,2H), 7.36(d,J=8.8Hz,2H), 7.55(t,J=8.0Hz,1H), 7.58(s,1H), 7.69(t,J=8.0Hz,1H), 7.91(d,J=8.0Hz,1H), 8.03(d,J=8.0Hz,1H).

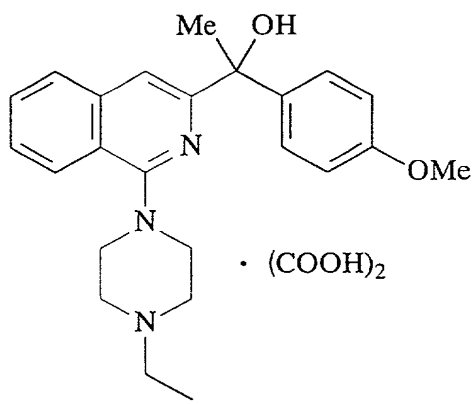
MS(FAB) m/z 378$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.74(br,4H), 3.55(br,4H), 3.80(s,3H), 5.18(d,J=4.8Hz,1H), 5.72(d,J=4.8Hz,1H), 6.87(d,J=8.8Hz,2H), 7.00(s,1H), 7.35(d,J=8.8Hz,2H), 7.45(ddd,J=8.4,8.0,1.2Hz,1H), 7.50(ddd,J=8.4,8.0,1.2Hz,1H), 7.63(d,J=8.0Hz,1H),

8.05(d,J=8.4Hz,1H).

Example 105 Synthesis of 3-[α-methyl-α-hydroxy-(4-methoxybenzyl)]-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



To a solution of 3-(4-methoxyphenylcarbonyl)-1-(4-ethylpiperazin-1-yl)isoquinoline (667 mg) in tetrahydrofuran (10 ml) was added a 3.0 M solution of methylmagnesium bromide in diethyl ether (1.8 ml) at 0 °C. The mixture was reacted at 0°C for further 10 min, and then the reaction solution was poured into an aqueous solution of saturated ammonium chloride, and was then extracted with ethyl acetate. The resulting organic layer was washed with water and brine, dried and evaporated. Then the resulting residue was purified by NH-silica gel column chromatography (ethyl acetate/hexane system), to give a yellow oil (643 mg, yield; 92%). The oil was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 179-181°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.20(t,J=7.6Hz,3H), 1.90(s,3H), 2.99(br,2H), 3.19(br,4H), 3.52(br,4H), 3.69(s,3H), 6.81(d,J=8.8Hz,2H), 7.48(d,J=8.8Hz,2H), 7.54(t,J=8.0Hz,1H), 7.66(s,1H), 7.67(t,J=8.0Hz,1H), 7.90(d,J=8.0Hz,1H), 8.02(d,J=8.0Hz,1H).

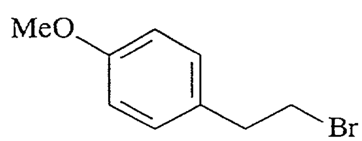
MS(FAB) m/z 392$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 1.95(s,3H), 2.53(q,J=7.2Hz,2H), 2.71(br,4H), 3.50(br,4H), 3.78(s,3H), 5.59(s,1H), 6.82(d,J=8.8Hz,2H), 7.15(s,1H), 7.43(d,J=8.8Hz,2H), 7.45(ddd,J=8.4,8.0,1.2Hz,1H), 7.57(ddd,J=8.4,8.0,1.2Hz,1H), 7.69(d,J=8.0Hz,1H), 8.04(d,J=8.4Hz,1H).

Example 106 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(4-methoxyphenethyl)isoquinoline

(106-1) 4-Methoxyphenethyl bromide

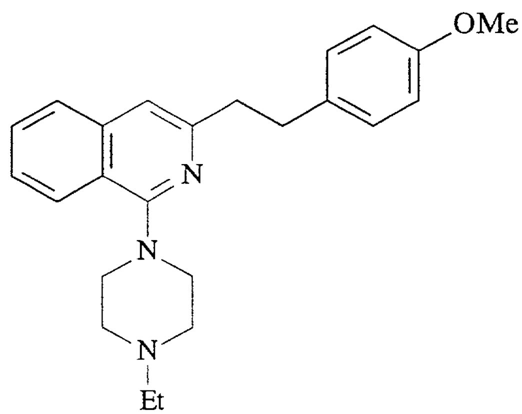


4-Methoxyphenethyl alcohol (50 g) and triphenylphosphine (103 g) were dissolved in methylene chloride (600 ml), followed by the addition of N-bromosuccinimide (70 g) in small portions under ice-cooling, and the resulting mixture was stirred at room temperature for 30 min. The reaction mixture was evaporated, and to the resulting residue was added hexane. The insoluble matters were filtered off, while the resulting filtrate was

evaporated, to give the title compound as a colorless oil (50.32 g, yield; 71%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 3.10(2H,t,J=7.6Hz), 3.53(2H,t,J=7.6Hz), 3.80(3H,s), 6.86(2H,d,J=8.8Hz), 7.13(2H,d,J=8.8Hz).

(106-2) 1-(1-Ethylpiperazin-4-yl)-3-(4-methoxyphenethyl)isoquinoline



Grignard reagent was prepared from magnesium (735 mg) and 4-methoxyphenethyl bromide (4.302 g) in a conventional manner. It was added dropwise into a solution of 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (961 mg) and [1,3-bis(diphenylphosphino)propane]nickel (II) chloride (49 mg) in tetrahydrofuran (15 ml), in nitrogen atmosphere under ice-cooling. After stirring the resulting mixture for 10 min, it was further stirred at room temperature for 3.5 hr. To the resulting mixture was added 1N hydrochloric acid (10 ml), followed by stirring for 10 min. Then, the mixture was basified with a 5N sodium hydroxide. The insoluble matters were filtered off through Celite, and then the resulting filtrate was

extracted with ethyl acetate. The resulting organic layer was washed with water, dried (over $MgSO_4$), evaporated and purified by (NH) silica gel column chromatography (ethyl acetate/hexane system). The resulting product was converted into a hydrochloride in a conventional manner, recrystallized from ethanol/isopropyl ether, to give the hydrochloride of the title compound as pale yellow crystals (346 mg, yield; 27%).

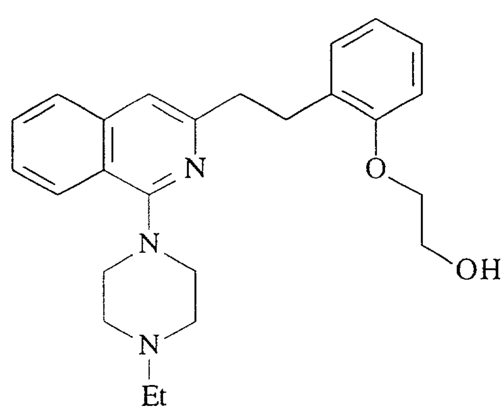
Hydrochloride:

m.p.; 224-227°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.32(3H,t,J=7.2Hz), 2.95-3.00(2H,m), 3.07-3.11(2H,m), 3.18(1H,q,J=7.2Hz), 3.20(1H,q,J=7.2Hz), 3.31(1H,t,J=10.4Hz), 3.34(1H,t,J=10.4Hz), 3.59(2H,d,J=10.4Hz), 3.60(2H,t,J=12.8Hz), 3.08(3H,s), 3.95(2H,d,J=12.8Hz), 6.80(2H,d,J=8.8Hz), 7.14(2H,d,J=8.8Hz), 7.32(1H,s), 7.59(1H,dd,J=8Hz,7Hz), 7.74(1H,dd,J=8Hz,7Hz,), 7.84(1H,d,J=8Hz), 8.09(1H,d,J=8Hz), 11.43(1H,br-s).

ESI-Mass; 376(MH^+).

Example 107 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(2-hydroxyethoxy)phenethyl]isoquinoline



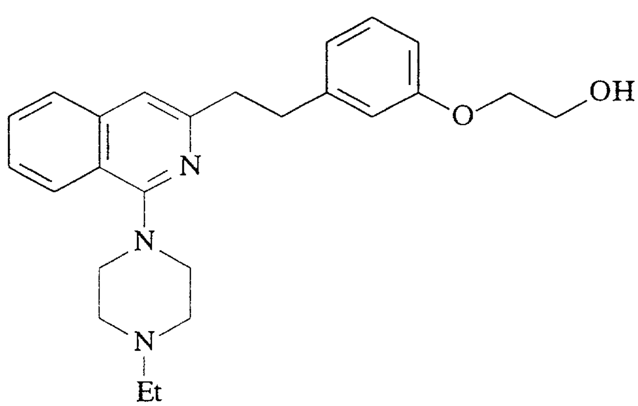
In the same manner as in Example 110, the oxalate of the title compound was obtained as a brown amorphous (209 mg, yield; 36%) from 1-(1-ethylpiperazin-4-yl)-3-[2-(2-hydroxyethoxy)phenylethynyl]isoquinoline (453 mg).

Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.23(3H,t,J=7.2Hz), 3.02(4H,s), 3.10(2H,q,J=7.2Hz), 3.26-3.36(4H,m), 3.46-3.62(4H,m), 3.73(2H,t,J=5Hz), 3.98(2H,t,J=5Hz), 6.77(1H,ddd,J=7.6Hz,7.4Hz.1.2Hz), 6.92(1H,dd,J=8Hz,1.2Hz), 7.07(1H,dd,J=7.4Hz,1.6Hz), 7.10(1H,ddd,J=8Hz,7.6Hz,1.6Hz), 7.23(1H,s), 7.51(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.64(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.7(1H,dd,J=8Hz,1.2Hz), 8.03(1H,dd,J=8Hz,1.2Hz).

ESI-Mass; 406(MH^+).

Example 108 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[3-(2-hydroxyethoxy)phenethyl]isoquinoline



In the same manner as in Example 110, the oxalate of the title compound was obtained as a colorless amorphous (218 mg, yield; 36%) from 1-(1-ethylpiperazin-4-yl)-3-[3-(2-

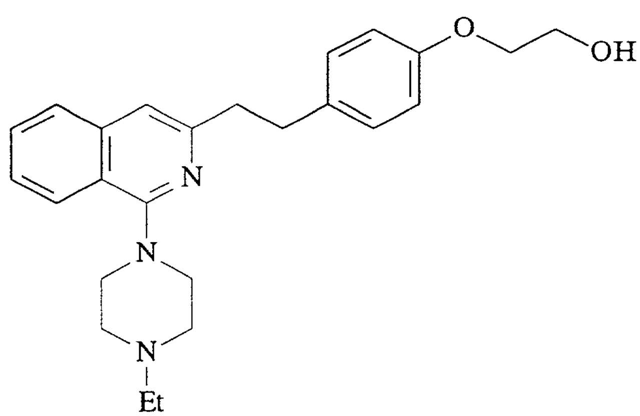
hydroxyethoxy)phenylethynyl]isoquinoline (454 mg).

Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.23(3H,t,J=7.2Hz), 3.00-3.04(4H,m), 3.09(2H,q,J=7.2Hz), 3.26-3.57(4H,m), 3.46-3.52(4H,m), 3.65(2H,t,J=5Hz), 3.89(2H,t,J=5Hz), 6.70(1H,dd,J=8Hz,2.5Hz), 6.76(1H,d,J=7.6Hz), 6.77(1H,d,J=2.5Hz), 7.12(1H,dd,J=8Hz,7.6Hz), 7.25(1H,s), 7.52(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.65(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.78(1H,d,J=8Hz), 8.04(1H,d,8Hz), 11.10(1H,br-s).

ESI-Mass; 406(MH$^+$).

Example 109 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[4-(2-hydroxyethoxy)phenethyl]isoquinoline



1-(1-Ethylpiperazin-4-yl)-3-[trans-4-(2-hydroxyethoxy)styryl]isoquinoline (722 mg) was dissolved in ethanol (16 ml), to which was then added Lindlar catalyst (1.4 g). Then, the resulting mixture was stirred in hydrogen atmosphere for 2 days. After the catalyst was filtered off, the resulting solution was evaporated and purified by (NH)silica gel column chromatography (ethyl acetate/hexane

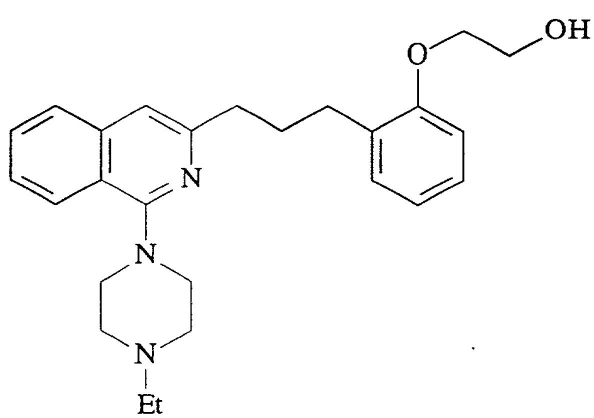
system). The resulting product was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as a pale brown amorphous (118 mg, yield; 11%).

Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.23(3H,t,J=7.2Hz), 2.99(2H,t,J=3.2Hz), 3.00(2H,t,J=3.2Hz), 3.10(2H,q,J=7.2Hz), 3.24-3.36(4H,m), 3.46-3.60(4H,m), 3.66(2H,t,J=5Hz), 3.89(2H,t,J=5Hz), 6.78(2H,d,J=8.8Hz), 7.09(2H,d,J=8.8Hz), 7.23(1H,s), 7.52(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.64(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.78(1H,d,J=8Hz), 8.04(1H,d,J=8Hz).

FAB-Mass; 406(MH^+).

Example 110 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-{3-[2-(2-hydroxyethoxy)phenyl]propyl}isoquinoline



1-(1-Ethylpiperazin-4-yl)-3-{3-[2-(2-hydroxyethoxy)phenyl]propyl}isoquinoline (619 mg) was converted into a hydrochloride, and then dissolved in ethanol (20 ml), to which was then added 10% palladium-carbon catalyst (1.25 g). The resulting mixture was stirred in hydrogen

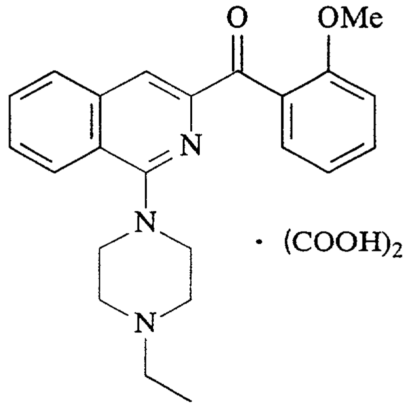
atmosphere overnight. After the catalyst was filtered off, the resulting solution was evapoareted. The reaction mixture was partitioned between ethyl acetate and 1N sodium hydroxide. The resulting organic layer was washed with water, dried (over $MgSO_4$), evaporated, and then purified by (NH) silica gel column chromatography (ethyl acetate/hexane system). The resulting product was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as a pale brown amorphous (200 mg, yield; 27%).

Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.22(3H,t,J=7.2Hz), 1.99(2H,qui,J=7.6Hz), 2.64(2H,t,J=7.6Hz), 2.76(2H,t,J=7.6Hz), 3.08(2H,q,J=7.2Hz), 3.26-3.34(4H,m), 3.42-3.60(4H,m), 3.68(2H,t,J=5.2Hz), 3.96(2H,t,J=5.2Hz), 6.84(1H,ddd,J=7.6Hz,7.4Hz,1.2Hz), 6.91(1H,dd,J=8Hz,1.2Hz), 7.12(1H,ddd,J=8Hz,7.6Hz,1.2Hz), 7.13(1H,dd,J=7.4Hz,1.6Hz), 7.26(1H,s), 7.51(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.65(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.81(1H,d,J=8Hz), 8.03(1H,d,J=8Hz).

ESI-Mass; 420(MH^+).

Example 111 Synthesis of 3-(2-methoxyphenylcarbonyl)-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



In the same manner as in Example 112, the free compound of the title compound was obtained (600 mg, yield; 60%) from 3-[α-hydroxy-(2-methoxybenzyl)]-1-(4-ethylpiperazin-1-yl)isoquinoline (1.0 g) and manganese dioxide (1.2 g).

The resulting free compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 153-156°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.20(t,J=7.2Hz,3H), 3.04(q,J=7.2Hz,2H), 3.22(br,4H), 3.42(br,4H), 3.63(s,3H), 7.08(t,J=8.0Hz,1H), 7.14(d,J=8.0Hz,1H), 7.43(dd,J=7.6,1.6Hz,1H), 7.54(dd,J=7.6,1.6Hz,1H), 7.78(t,J=7.6Hz,1H), 7.84(t,J=7.6Hz,1H), 8.16(d,J=7.6Hz,1H), 8.19(d,J=7.6Hz,1H).

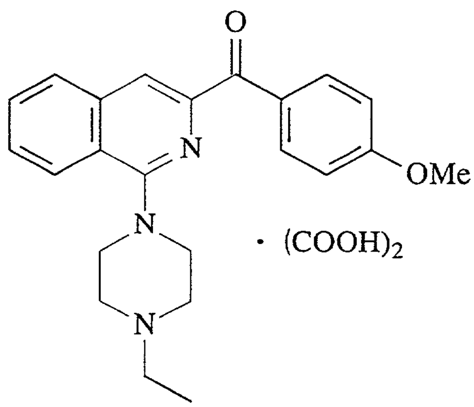
MS(FAB) m/z 376(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.12(t,J=7.2Hz,3H), 2.48(q,J=7.2Hz,2H), 2.62(br,4H), 3.36(br,4H), 3.69(s,3H),

6.96(d,J=8.4Hz,1H), 7.03(dt,J=7.6,0.8Hz,1H), 7.45(ddd,J=8.4,7.6,1.6Hz,1H), 7.55(dd,J=7.6,1.6Hz,1H), 7.61(ddd,J=8.4,8.0,1.2Hz,1H), 7.66(ddd,J=8.4,8.0,1.2Hz,1H), 7.92(d,J=8.0Hz,1H), 8.06(s,1H), 8.09(d,J=8.4Hz,1H).

Example 112 Synthesis of 3-(4-methoxyphenylcarbonyl)-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



3-[α-Hydroxy-(4-methoxybenzyl)]-1-(4-ethylpiperazin-1-yl)isoquinoline (1.1 g) was dissolved in a mixture solution of benzene (20 ml) and methylene chloride (20 ml), followed by the addition of manganese dioxide (1.3 g). After the mixture was reacted under stirring at room temperature overnight, it was filtered and evaporated. The resulting crystals were washed with diethyl ether, to give the free compound of the title compound as a white solid (765 mg, yield; 70%). The resulting free compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 176-179°C

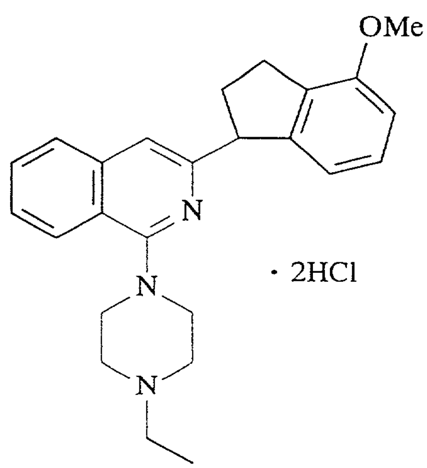
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.21(t,J=7.2Hz,3H), 3.01(br,2H), 3.24(br,2H), 3.59(br,6H), 3.87(s,3H), 7.08(d,J=8.8Hz,2H), 7.79(t,J=8.0Hz,1H), 7.84(t,J=8.0Hz,1H), 8.11(d,J=8.8Hz,2H), 8.13(s,1H), 8.17(d,J=8.0Hz,1H), 8.21(d,J=8.0Hz,1H).

MS(FAB) m/z 376$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.6Hz,3H), 2.54(q,J=7.6Hz,2H), 2.73(br,4H), 3.51(br,4H), 3.91(s,3H), 6.96(d,J=8.8Hz,2H), 7.62(ddd,J=8.4,8.0,1.2Hz,1H), 7.68(ddd,J=8.4,8.0,1.2Hz,1H), 7.92(d,J=8.0Hz,1H), 8.06(s,1H), 8.14(d,J=8.4Hz,1H), 8.29(d,J=8.8Hz,2H).

Example 113 Synthesis of 3-(4-methoxyindan-1-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manner as in Example 104, a yellow compound was obtained (440 mg, yield; 98%) from 5-methoxy-1-indanone (608 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (800 mg). The resulting compound was converted into a

hydrochloride in a conventional manner, to give the title compound as white crystals.

Hydrochloride:

m.p.; 108-110°C

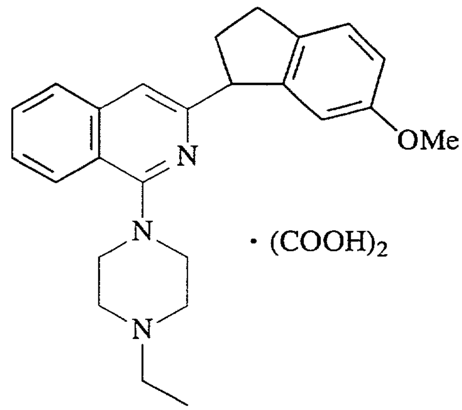
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.29(t,J=7.2Hz,3H), 2.39-2.46(m,1H), 2.48-2.82(m,1H), 2.83-2.89(m,1H), 2.99-3.07(m,1H), 3.14-3.24(m,4H), 3.40-3.58(m,4H), 3.76-3.90(m,2H), 3.80(s,3H), 4.58(t,J=7.2Hz,1H), 6.67(d,J=8.0Hz,1H), 6.79(d,J=8.0Hz,1H), 7.10(t,J=8.0Hz,1H), 7.30(s,1H), 7.58(t,J=8.4Hz,1H), 7.71(t,J=8.4Hz,1H), 7.86(d,J=8.4Hz,1H), 8.07(d,J=8.4Hz,1H).

MS(FAB) m/z 388(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.15(t,J=7.2Hz,3H), 2.17-2.61(m,2H), 2.51(q,J=7.2Hz,2H), 2.68(br,4H), 2.88-2.96(m,1H), 3.08-3.15(m,1H), 3.44(br,4H), 3.86(s,3H), 4.54(t,J=7.2Hz,1H), 6.70(d,J=7.6Hz,1H), 6.79(d,J=7.6Hz,1H), 7.02(s,1H), 7.10(t,J=7.6Hz,1H), 7.40(ddd,J=8.4,8.0,1.2Hz,1H), 7.52(ddd,J=8.4,8.0,1.2Hz,1H), 7.64(d,J=8.0Hz,1H), 8.02(d,J=8.4Hz,1H).

Example 114 Synthesis of 3-(6-methoxyindan-1-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



In the same manner as in Example 104, an oil was obtained from 6-methoxy-1-indanone (713 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (937 mg). Methanol (20 ml) and platinum oxide (20 mg) were added to the oil (387 mg), and the mixture was reacted in hydrogen atmosphere overnight. The resulting reaction solution was filtered through Celite, and then evaporated. The resulting residue was purified by NH-silica gel column chromatography, to give a yellow oil (307 mg, yield; 79%). The oil was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 122-124°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.22(t,J=7.2Hz,3H), 2.34-2.42(m,1H), 2.44-2.54(m,1H), 2.82-2.93(m,1H), 3.02-3.10(m,4H), 3.30(br,4H), 3.53(br,5H), 3.64(s,3H), 4.48(t,J=7.2Hz,1H), 6.64(d,J=2.4Hz,1H), 6.74(dd,J=8.0,2.4Hz,1H), 7.19(d,J=8.0Hz,1H), 7.32(s,1H), 7.56(t,J=8.0Hz,1H), 7.69(t,J=8.0Hz,1H), 7.86(d,J=8.0Hz,1H),

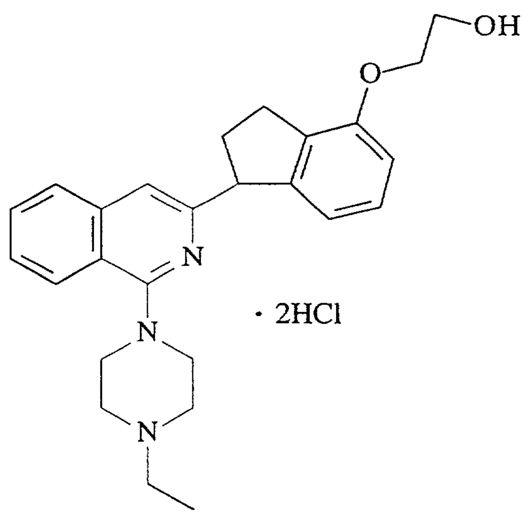
8.06(d,J=8.0Hz,1H).

MS(FAB) m/z 388$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.15(t,J=7.2Hz,3H), 2.41-2.61(m,2H), 2.52(q,J=7.2Hz,2H), 2.69(br,4H), 2.86-2.93(m,1H), 3.12-3.04(m,1H), 3.45(br,4H), 3.71(s,3H), 4.49(t,J=7.2Hz,1H), 6.72(d,J=2.4Hz,1H), 6.73(dd,J=8.0,2.4Hz,1H), 7.03(s,1H), 7.18(d,J=8.0Hz,1H), 7.41(ddd,J=8.4,8.0,1.2Hz,1H), 7.53(ddd,J=8.4,8.0,1.2Hz,1H), 7.64(d,J=8.0Hz,1H), 8.03(d,J=8.4Hz,1H).

Example 115 Synthesis of 3-[4-(2-hydroxyethoxy)indan-1-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manner as in Example 104, an oil was obtained from 5-(2-t-butyldimethylsilyloxyethoxy)-1-indanone (1.1 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (800 mg). To a solution of the oil in tetrahydrofuran (10 ml) was added a 1.0 M solution of tetrabutylammonium fluoride in

tetrahydrofuran (6 ml), and the mixture was stirred at room temperature for 30 min. The reaction solution was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system), to give the free compound of the title compound as a colorless oil (394 mg, yield; 36%). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as a white amorphous.

Hydrochloride (amorphous):

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.28(t,J=7.2Hz,3H), 2.38-2.41(m,1H), 2.45-2.50(m,1H), 2.83-2.93(m,1H), 3.00-3.11(m,1H), 3.14-3.30(m,4H), 3.45-3.60(m,4H), 3.76(t,J=4.8Hz,2H), 3.82-3.91(m,1H), 4.03(br,2H), 4.58(t,J=7.2Hz,2H), 6.66(d,J=8.0Hz,1H), 6.78(t,J=8.0Hz,1H), 7.08(t,J=8.0Hz,1H), 7.28(s,1H), 7.58(t,J=8.0Hz,1H), 7.71(t,J=8.0Hz,1H), 7.86(d,J=8.0Hz,1H), 8.07(d,J=8.0Hz,1H).

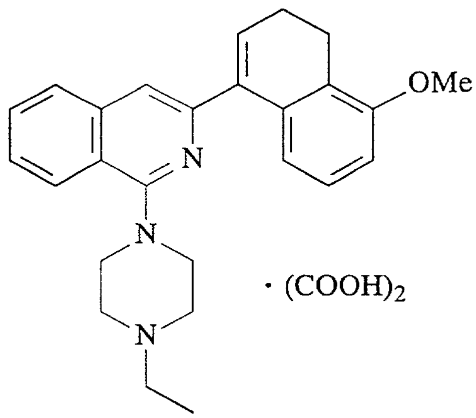
MS(FAB) m/z 418$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.45(t,J=7.2Hz,3H), 2.43-2.61(m,2H), 2.53(q,J=7.2Hz,2H), 2.69(br,4H), 2.89-2.97(m,1H), 3.09-3.17(m,1H), 3.44(br,4H), 3.99(t,J=4.0Hz,2H), 4.13-4.16(m,2H), 4.54(t,J=7.6Hz,1H), 6.71(d,J=7.6Hz,1H), 6.81(d,J=7.6Hz,1H), 7.03(s,1H), 7.09(t,J=7.6Hz,1H), 7.41(ddd,J=8.4,8.0,1.2Hz,1H), 7.53(ddd,J=8.4,8.0,1.2Hz,1H),

7.64(d,J=8.0Hz,1H), 8.03(d,J=8.4Hz,1H).

Example 116 Synthesis of 3-(8-methoxy-1,2-dihydronaphthalen-4-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



In the same manner as in Example 104, a brown oil was obtained (97 mg, yield; 93%) from 5-methoxy-1-tetralone (711 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (860 mg). The resulting oil was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 136-139°C

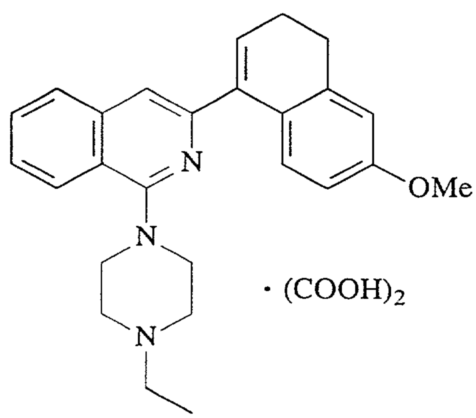
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.22(t,J=7.2Hz,3H), 2.36(br,2H), 2.77(t,J=8.0Hz,2H), 3.06(br,2H), 3.28(br,4H), 3.52(br,4H), 3.83(s,3H), 6.52(t,J=4.4Hz,1H), 6.79(d,J=8.0Hz,1H), 6.93(d,J=8.0Hz,1H), 7.11(t,J=8.0Hz,1H), 7.53(s,1H), 7.61(t,J=8.0Hz,1H), 7.72(t,J=8.4Hz,1H), 7.93(d,J=8.4Hz,1H), 8.12(d,J=8.4Hz,1H).

MS(FAB) m/z 400(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz, $CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 2.40-2.45(m,2H), 2.54(q,J=7.2Hz,2H), 2.73(br,4H), 2.88(t,J=8.0Hz,2H), 3.52(br,4H), 3.88(s,3H), 6.60(t,J=4.4Hz,1H), 6.82(d,J=8.0Hz,1H), 6.99(d,J=8.0Hz,1H), 7.09(t,J=8.0Hz,1H), 7.35(s,1H), 7.46(dt,J=8.4,1.2Hz,1H), 7.57(dt,J=8.4,1.2Hz,1H), 7.71(d,J=8.4Hz,1H), 8.08(d,J=8.4Hz,1H).

Example 117 Synthesis of 3-(7-methoxy-1,2-dihydronaphthalen-4-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



To a solution of 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (860 mg) in tetrahydrofuran (10 ml) was added 2.5 M n-butyl lithium (1.3 ml) at -78°C. Thereafter, the mixture was raised to -40°C, to which was then added 6-methoxy-1-tetralone (711 mg), and then the mixture was stirred at -40°C for 20 min. The reaction solution was poured into an aqueous solution of saturated ammonium chloride and extracted with ethyl acetate. The resulting organic layer was washed with

water and brine, dried and evaporated. Then, to the resulting residue were added methanol (10 ml) and 5N hydrochloric acid (1 ml), and the mixture was heated under reflux for 1 hr. The reaction solution was basified by adding a 2N aqueous solution of sodium hydroxide thereto, which was then partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and evaporated. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system), to give free compound of the title compound as a colorless oil (410 mg, yield; 86%). The free compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 112-114°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.24(br,3H), 2.39(br,2H), 2.51(br,2H), 2.78(br,2H), 3.13(br,2H), 3.33(br,2H), 3.76(br,4H), 6.40(s,1H), 6.71(d,J=8.4Hz,1H), 6.87(s,1H), 7.14(d,J=8.4Hz,1H), 7.57(s,1H), 7.62(t,J=8.0Hz,1H), 7.73(t,J=8.0Hz,1H), 7.94(d,J=8.0Hz,1H), 8.12(d,J=8.0Hz,1H).

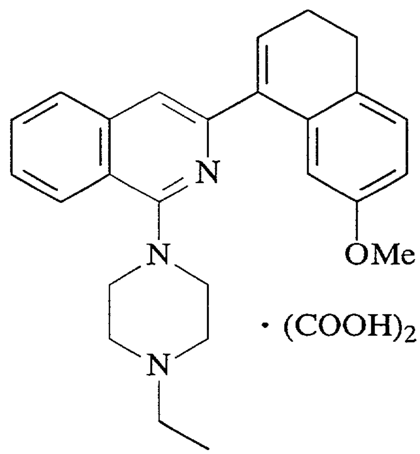
MS(FAB) m/z 400$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 2.42-2.47(m,2H), 2.54(q,J=7.2Hz,2H), 2.73(br,4H), 2.85(t,J=7.6Hz,2H), 3.51(br,4H), 3.82(s,3H), 6.47(t,J=4.8Hz,1H), 6.67(dd,J=8.8,2.8Hz,1H), 6.79(d,J=2.8Hz,1H), 7.32(d,J=8.8Hz,1H), 7.44(s,1H),

7.46(ddd,J=8.4,8.0,1.2Hz,1H), 7.57(ddd,J=8.4,8.0,1.2Hz,1H), 7.71(d,J=8.0Hz,1H), 8.08(d,J=8.4Hz,1H).

Example 118 Synthesis of 3-(6-methoxy-1,2-dihydronaphthalen-4-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



In the same manner as in Example 104, the free compound of the title compound was obtained as a colorless oil (97 mg, yield; 98%) from 7-methoxy-1-tetralone and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline. The free compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 150-153°C

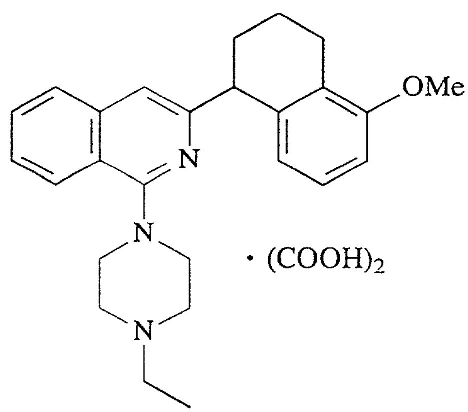
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.24(t,J=7.2Hz,3H), 2.38(br,2H), 2.74(t,J=7.6Hz,2H), 3.11(br,2H), 3.35(br,4H), 3.55(br,4H), 3.63(s,3H), 6.55(t,J=4.4Hz,1H), 6.78-6.79(m,2H), 7.18(d,J=8.4Hz,1H), 7.59(s,1H), 7.62(t,J=8.0Hz,1H), 7.73(t,J=8.0Hz,1H), 7.96(d,J=8.0Hz,1H), 8.13(d,J=8.0Hz,1H).

MS(FAB) m/z 400$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz, $CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 2.42-2.47(m,2H), 2.54(q,J=7.2Hz,2H), 2.73(br,4H), 2.80(t,J=8.0Hz,2H), 3.52(br,4H), 3.70(s,3H), 6.60(t,J=4.8Hz,1H), 6.73(dd,J=8.0,2.8Hz,1H), 6.96(d,J=2.8Hz,1H), 7.13(d,J=8.0Hz,1H), 7.38(s,1H), 7.46(ddd,J=8.4,8.0,1.2Hz,1H), 7.57(ddd,J=8.4,8.0,1.2Hz,1H), 7.72(d,J=8.0Hz,1H), 8.08(d,J=8.4Hz,1H).

Example 119 Synthesis of 3-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



In the same manner as in Example 18, the free compound of the title compound was obtained as a colorless oil (218 mg, yield; 83%) from 3-(8-methoxy-1,2-dihydronaphthalen-4-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline (273 mg) and palladium/carbon catalyst (20 mg). The free compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 133-136°C

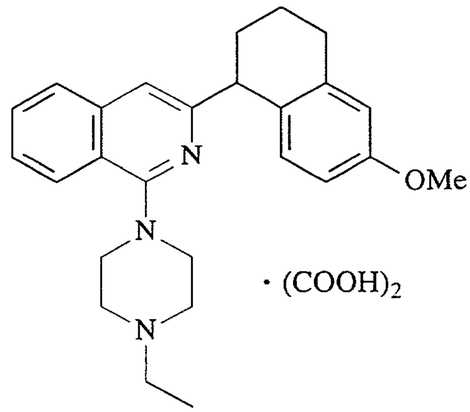
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.23(t,J=7.2Hz,3H), 1.65-1.80(m,3H), 2.00(br,1H), 2.15(br,1H), 2.55-2.72(m,2H), 3.11(d,J=5.6Hz,2H), 3.32(br,2H), 3.54(br,1H), 3.60(br,2H), 3.80(s,3H), 3.93(br,2H), 4.24(t,J=5.6Hz,1H), 6.52(d,J=8.0Hz,1H), 6.79(d,J=8.0Hz,1H), 6.95(s,1H), 7.04(t,J=8.0Hz,1H), 7.55(t,J=8.0Hz,1H), 7.66(t,J=8.0Hz,1H), 7.78(d,J=8.0Hz,1H), 8.06(d,J=8.0Hz,1H).

MS(FAB) m/z 402$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.6Hz,3H), 1.68-1.75(m,2H), 2.01-2.09(m,1H), 2.23-2.29(m,1H), 2.53(q,J=7.6Hz,2H), 2.62-2.84(m,2H), 2.70(br,4H), 3.47(br,4H), 3.87(s,3H), 4.29(t,J=5.6Hz,1H), 6.67(d,J=8.0Hz,1H), 6.70(s,1H), 6.72(d,J=8.0Hz,1H), 7.06(t,J=8.0Hz,1H), 7.40(ddd,J=8.4,8.0,1.2Hz,1H), 7.49(ddd,J=8.4,8.0,1.2Hz,1H), 7.56(d,J=8.0Hz,1H), 8.03(d,J=8.4Hz,1H).

Example 120 Synthesis of 3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



Methanol (30 ml) and platinum oxide (30 mg) were added to 3-(6-methoxy-1,2-dihydronapthalen-1-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline (347 mg), and the mixture was reacted in hydrogen atmosphere for 6 hr. The resulting reaction solution was filtered through Celite, and then evaporated. The resulting residue was purified by NH-silica gel column chromatography, to give the free compound of the title compound as an oil (189 mg, yield; 54%). The resulting free compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 170-173°C

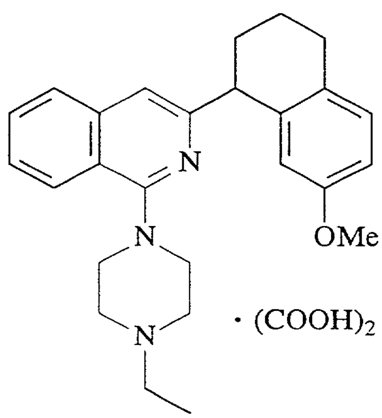
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.21(br,3H), 1.60-1.80(m,2H), 1.95-2.20(m,2H), 2.81(br,2H), 3.04(br,2H), 3.23(br,4H), 3.49(br,4H), 3.72(s,3H), 4.19(br,1H), 6.64(d,J=8.4Hz,1H), 6.73(s,1H), 6.82(d,J=8.4Hz,1H), 6.96(s,1H), 7.55(t,J=8.0Hz,1H), 7.65(t,J=8.0Hz,1H), 7.78(d,J=8.0Hz,1H), 8.05(d,J=8.0Hz,1H).

MS(FAB) m/z 402(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 2.05-2.14(m,3H), 2.18-2.26(m,1H), 2.51(q,J=7.2Hz,2H), 2.71(br,4H), 2.71-2.89(m,2H), 3.47(br,4H), 3.81(s,3H), 4.25(t,J=5.6Hz,1H), 6.66(dd,J=8.4,2.8Hz,1H), 6.70(d,J=2.8Hz,1H), 6.72(s,1H), 6.94(d,J=8.4Hz,1H), 7.40(ddd,J=8.4,8.0,1.2Hz,1H), 7.50(ddd,J=8.4,8.0,1.2Hz,1H), 7.57(d,J=8.0Hz,1H), 8.03(d,J=8.4Hz,1H).

Example 121 Synthesis of 3-(7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



In the same manner as in Example 18, the free compound of the title compound was obtained as a colorless oil (239 mg, yield; 61%) from 3-(6-methoxy-1,2-dihydronaphthalen-4-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline (405 mg) and palladium/carbon catalyst (30 mg). The free compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 110-112°C

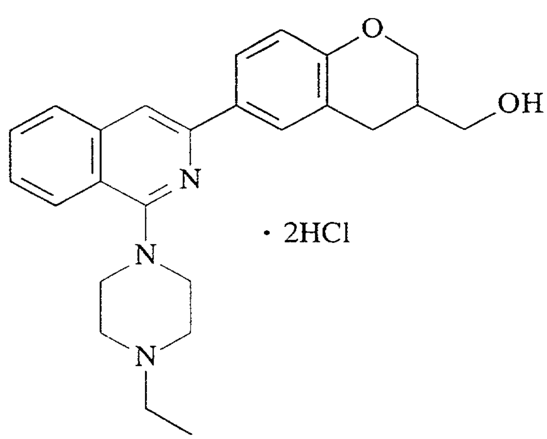
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.21(br,3H), 1.73(br,2H), 2.02(br,1H), 2.12(br,1H), 2.73(br,2H), 3.09(br,2H), 3.29(br,4H), 3.50(br,4H), 3.58(s,3H), 4.21(br,1H), 6.43(s,1H), 6.72(d,J=8.4Hz,1H), 6.97(s,1H), 7.06(d,J=8.4Hz,1H), 7.53(t,J=8.0Hz,1H), 7.64(t,J=8.0Hz,1H), 7.77(d,J=8.0Hz,1H), 8.04(d,J=8.0Hz,1H).

MS(FAB) m/z 402$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 1.66-1.81(m,2H), 2.05-2.13(m,1H), 2.21-2.28(m,1H), 2.52(q,J=7.2Hz,2H), 2.71(br,4H), 2.71-2.85(m,2H), 3.47(br,4H), 3.67(s,3H), 4.27(t,J=6.0Hz,1H), 6.58(d,J=2.4Hz,1H), 6.74(s,1H), 6.75(dd,J=8.8,2.4Hz,1H), 7.08(d,J=8.4Hz,1H), 7.41(dt,J=8.4,1.2Hz,1H), 7.51(dt,J=8.4,1.2Hz,1H), 7.59(d,J=8.4Hz,1H), 8.03(d,J=8.4Hz,1H).

Example 122 Synthesis of 3-(3-hydroxymethylchroman-6-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, an oil was obtained from 6-bromo-3-acetoxymethylchroman (4.67 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (2.2 g). To the resulting oil were added methanol (20 ml) and a 1N aqueous solution of sodium hydroxide (2 ml), and then reacted at 50°C for 2 hr. The reaction solution was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography, to give the free compound of the title compound as an oil. The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals (1.93 g, yield; 91%).

Hydrochloride:

m.p.; 168-172°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 2.13(br,1H), 2.63(dd,J=16.4,4.8Hz,1H), 2.89(dd,J=16.4,5.2Hz,1H), 3.19-3.26(m,2H), 3.33-3.43(m,3H), 3.48-3.60(m,3H), 3.62(d,J=11.6Hz,2H), 3.90-3.98(m,3H), 4.31(dd,J=11.2,2.0Hz,1H), 6.87(d,J=9.2Hz,1H), 7.56(t,J=8.0Hz,1H), 7.71(t,J=8.0Hz,1H), 7.91-7.96(m,4H), 8.09(d,J=8.0Hz,1H).

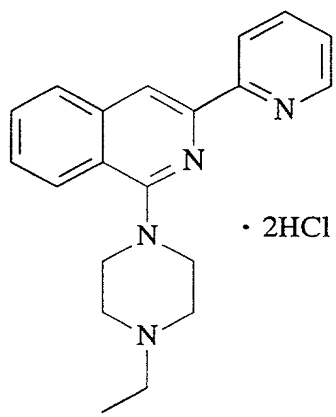
MS(FAB) m/z 404(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.30-2.36(m,1H), 2.56(q,J=7.2Hz,2H), 2.66-2.73(m,1H), 2.76(br,4H),

2.98(dd,J=16.4,1.2Hz,1H), 3.57(br,4H), 3.78-3.69(m,2H), 4.05-4.13(m,1H), 4.33-4.37(m,1H), 6.89(d,J=8.0Hz,1H), 7.42(ddd,J=8.4,8.0,1.2Hz,1H), 7.56(ddd,J=8.4,8.0,1.2Hz,1H), 7.59(s,1H), 7.75(d,J=8.0Hz,1H), 7.88(dd,J=8.0,2.0Hz,1H), 7.89(s,1H), 8.05(d,J=8.4Hz,1H).

Example 123 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(2-pyridyl)isoquinoline dihydrochloride or compound identified by the following analytical data and synthetic procedures



3-(2-Pyridyl)isoquinolin-1-one obtained by reacting N-methyl-o-toluamide (2.28 g) and 2-cyanopyridine (1.59 g) according to Example 10-1 was added to phosphorus oxychloride (10 ml), and the mixture was stirred at 100°C for 3 hr. The reaction solution was evaporated, and then ethyl acetate and water were added to the resulting residue. The resulting organic layer was washed with water, an aqueous solution of sodium bicarbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting 1-chloro-3-(2-pyridyl)isoquinoline was reacted with N-ethylpiperazine (15 ml) at 110°C for 12 hr. The reaction solution was evaporated,

and then ethyl acetate and water were added to the resulting residue. The resulting organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the free compound of the title compound as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=8.0Hz,3H), 2.57(q,J=8.0Hz,2H), 2.78(m,4H), 3.58(m,4H), 7.27(m,1H), 7.50(t,J=9.2Hz,1H), 7.61(t,J=9.2Hz,1H), 7.81(t,J=9.2Hz,1H), 7.89(d,J=9.2Hz,1H), 8.10(d,J=9.2Hz,1H), 8.40(s,1H), 8.52(d,J=9.2Hz,1H), 8.67(d,J=4.5Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 0.31 g of the title compound as a yellow powder.

Hydrochloride:

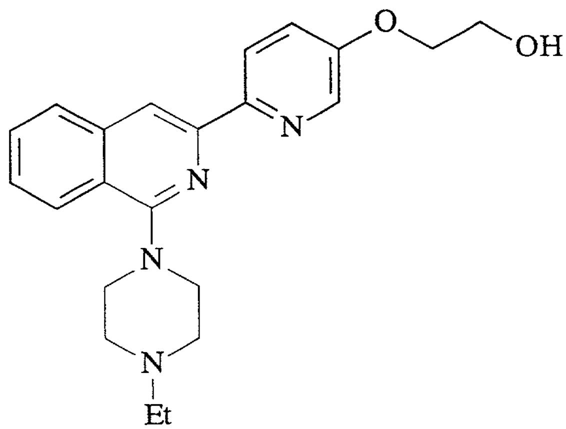
m.p.; 160-162°C

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.34(t,J=7.2Hz,3H), 3.19-3.28(m,2H), 3.31-3.43(m,2H), 3.55-3.70(m,4H), 4.14(br-d,2H), 7.71-7.79(m,2H), 7.84(t,J=8.0Hz,1H), 8.10(d,J=8.0Hz,1H), 8.20(d,J=8.0Hz,1H), 8.30-8.39(m,1H), 8.63(s,1H), 8.66(d,J=8.0Hz,1H), 8.85(br-d,1H), 11.26(br-s,1H).

MS(FAB) m/z 319$(M+H)^+$.

Example 124 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[5-(2-

hydroxyethoxy)pyridin-2-yl]isoquinoline



In the same manner as in Example 127-1, 5-(2-acetoxyethoxy)-2-tributylstannylpyridine was obtained as a colorless solid (3.362 g) from a mixture (4.015 g) of 2-iodo-3-hydroxypyridine and 4-iodo-3-hydroxypyridine, 2-bromoethyl acetate (4.551 g) and bis(tributyltin) (13.6 ml). The resulting compound and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (452 mg)were treated in the same manner as in Example 300, to give the hydrochloride of the title compound as yellow crystals (recrystallized from ethanol/isopropyl ether) (189 mg, yield; 29%).

Hydrochloride:

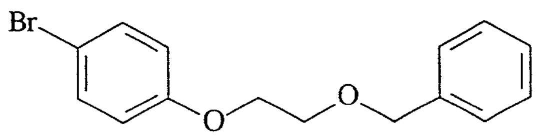
m.p.; 110-115°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.30(3H,t,J=7.2Hz), 3.20(1H,q,J=7.2Hz), 3.22(1H,q,J=7.2Hz), 3.30-3.40(2H,m), 3.48-3.60(4H,m), 3.80-3.90(2H,m), 4.17(2H,d,J=13.2Hz), 4.30-4.40(2H,m), 7.75(1H,dd,J=8Hz,7Hz), 7.76-7.88(1H,m), 7.84(1H,dd,J=8H,7Hz), 8.07(1H,d,J=8Hz), 8.19(1H,d,J=8Hz), 8.16-8.30(1H,m), 8.44-8.60(2H,m).

ESI-Mass; 379(MH^+).

Example 125 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(2-hydroxyethoxy)pyridin-5-yl]isoquinoline

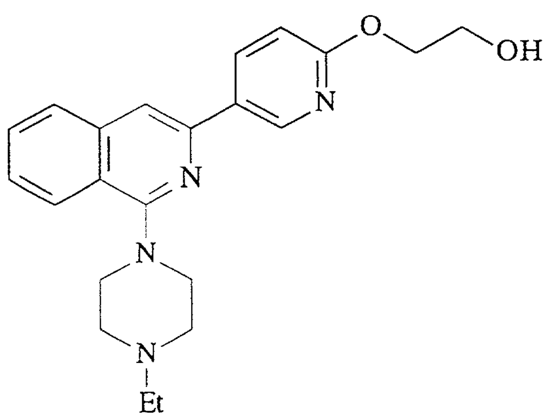
(125-1) 2-(2-Benzyloxyethoxy)-5-bromopyridine



In the same manner as in Example 126-1, 2.705 g of the title compound was obtained as a yellow oil from 2-benzyloxyethanol (15.219 g) and 2,5-dibromopyridine (2.369 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 3.81(2H,t,J=4.8Hz), 4.46(2H,t,J=4.8Hz), 4.61(2H,s), 6.72(1H,d,J=8.8Hz), 7.27-7.36(5H,m), 7.64(1H,dd,J=8.8Hz,2.4Hz), 8.16(1H,d,J=2.4Hz).

(125-2) 1-(1-Ethylpiperazin-4-yl)-3-[2-(2-hydroxyethoxy)pyridin-5-yl]isoquinoline



According to Example 167-2, 2-(2-benzyloxyethoxy)-5-bromopyridine (1.233 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (480 mg) were treated, which were continuously treated in the same manner as in Example 167-3,

to give the hydrochloride of the title compound. The resulting hydrochloride was recrystallized from ethanol/isopropyl ether, to give the title compound as pale yellow crystals (186 mg, yield; 27%).

Hydrochloride:

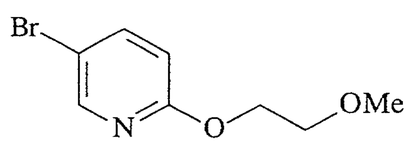
m.p.; 137-142°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.31(3H,t,J=7.2Hz), 3.16-3.24(2H,m), 3.30(1H,t,J=10.4Hz), 3.33(1H,t,J=10.4Hz), 3.54(2H,t,J=13.6Hz), 3.58(2H,d,J=10.4Hz), 3.73(2H,t,J=5.2Hz), 3.99(2H,d,J=13.6Hz), 4.33(2H,t,J=5.2Hz), 6.96(1H,d,J=8.8Hz), 7.58(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.73(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.93(1H,d,J=8Hz), 8.04(1H,s), 8.09(1H,d,J=8Hz), 8.46(1H,dd,J=8.8Hz,2.8Hz), 8.96(1H,d,J=2.8Hz), 11.15(1H,br-s).

ESI-Mass; 379(MH^+).

Example 126 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(2-methoxyethoxy)pyridin-5-yl]isoquinoline

(126-1) 2-(2-Methoxyethoxy)-5-bromopyridine

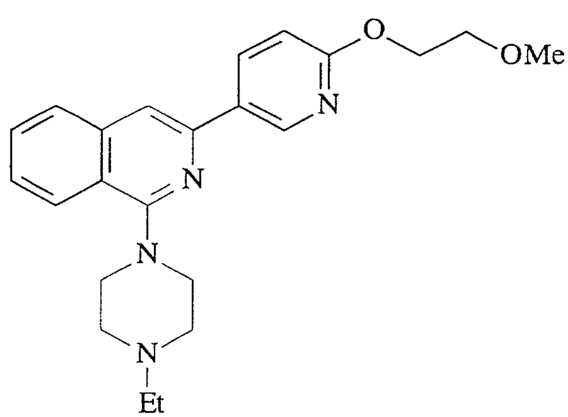


2-Methoxyethanol (7.9 mg) was dissolved in N,N-dimethylformamide (50 ml), followed the by addition of 60% sodium hydride (4 g) under ice-cooling, and the mixture was stirred for 20 min. Thereafter, it was stirred at 90°C for further 30 min. To the reaction mixture was added dropwise

2,5-dibromopyridine (2.369 g)/N,N-dimethylformamide (20 ml) solution, and the mixture was stirred overnight. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a colorless oil (1.122 g, yield; 48%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 3.43(3H,s), 3.73(2H,t,J=4.6Hz), 4.44(2H,t,4.6Hz), 6.72(1H,dd,J=8.8Hz,0.8Hz), 7.64(1H,dd,J=8.8Hz,2.4Hz), 8.17(1H,dd,J=2.4Hz,0.8Hz).

(126-2) 1-(1-Ethylpiperazin-4-yl)-3-[2-(2-methoxyethoxy)pyridin-5-yl]isoquinoline



In the same manner as in Example 167-2, the hydrochloride of the title compound was obtained as yellow crystals (371 mg, yield; 53%) from 2-(2-methoxyethoxy)-5-bromopyridine (928 mg) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (480 mg).

Hydrochloride:

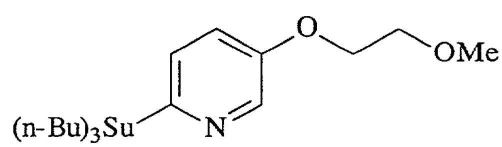
m.p.; 115-120°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(3H,t,J=7.2Hz), 3.18-3.65(2H,m), 3.70(2H,t,J=4.6Hz), 4.02(2H,d,J=13.6Hz), 4.45(2H,t,J=4.6Hz), 6.99(1H,d,J=8.4Hz), 7.61(1H,dd,J=8.4Hz,7Hz), 7.75(1H,dd,J=8.4Hz,7Hz), 7.96(1H,d,J=8.4Hz), 8.07(1H,s), 8.12(1H,d,J=8.4Hz), 8.48(1H,dd,J=8.4Hz,2.8Hz), 8.99(1H,s,J=2.8Hz).

ESI-Mass; 393(MH^+).

Example 127 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[5-(2-methoxyethoxy)pyridin-2-yl]isoquinoline

(127-1) 5-Methoxyethoxy-2-tributylstannylpyridine

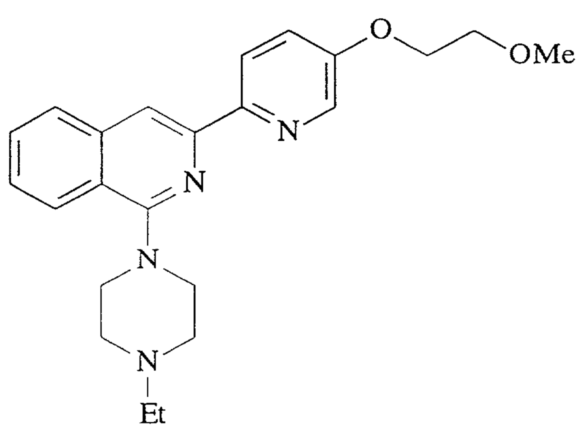


3-Hydroxypyridine (20.077 g) was dissolved in methanol (350 ml), sodium iodide (31.565 g) and sodium hydroxide (8.545 g) were added thereto, 5% sodium hypochlorite (314 mg) was added thereto under ice-cooling, and then the mixture was stirred for 5 hr. 10% sodium thiosulfate solution (200 ml) was added to the reaction mixture, which was then neutralized with 5N hydrochloric acid and extracted with ethyl acetate. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give a mixture of 2-iodo-3-hydroxypyridine and 4-iodo-3-hydroxypyridine (7:3) as a a yellow solid (12.544 g). The resulting mixture (2.97 g) was dissolved in N,N-

dimethylformamide (40 ml), followed by the addition of 2-bromoethyl methyl ether (3.822 g) and potassium carbonate (3.704 g), and the mixture was stirred at 80°C overnight. The resulting insoluble matters were filtered off. The resulting reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue and bis(tributyltin) (5 ml) were treated in the same manner as in Example 161-2, to give 1.142 g of the title compound as a colorless oil.

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.87(9H,t,J=7.4Hz), 1.11-1.16(6H,m), 1.29-1.37(6H,m), 1.50-1.61(6H,m), 3.43(3H,s), 3.74(2H,t,J=5Hz), 4.06(2H,t,J=5Hz), 6.97(1H,dd,J=8.4Hz,1.2Hz), 7.08(1H,dd,J=8.4Hz,4.8Hz), 8.37(1H,dd,J=4.8Hz,1.2Hz).

<u>(127-2) 1-(1-Ethylpiperazin-4-yl)-3-[5-(2-methoxyethoxy)pyridin-2-yl]isoquinoline</u>



In the same manner as in Example 161-3, the hydrochloride of the title compound was obtained as yellow crystals

(recrystallized form ethanol/isopropyl ether) (225 mg, yield; 36%) from 5-(2-methoxyethoxy)-2-tributylstannylpyridine (1.142 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (448 mg).

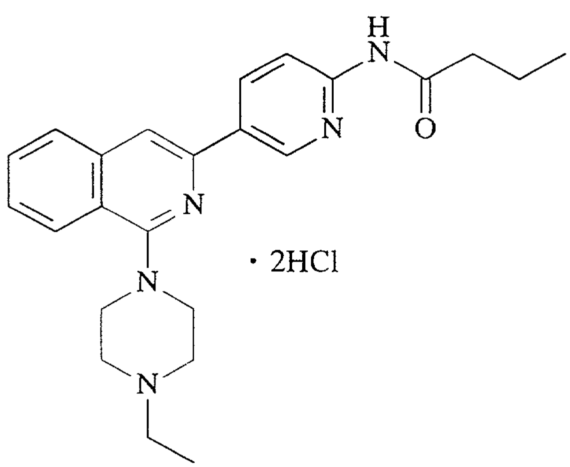
Hydrochloride:

m.p.; 116-119°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.31(3H,t,J=7.2Hz), 3.15-3.25(2H,m), 3.30-3.40(2H,m), 3.37(3H,s), 3.54-3.62(4H,m), 3.80-3.85(2H,m), 4.20(2H,d,J=14Hz), 4.45-4.52(2H,m), 7.77(1H,dd,J=8Hz,7Hz), 7.86(1H,dd,J=8Hz,7Hz), 7.88-7.96(1H,m), 8.03(1H,d,J=8Hz), 8.20(1H,d,J=8Hz), 8.24-8.36(1H,m), 8.50-8.60(2H,m).

ESI-Mass; 393(MH^{+}).

Example 128 Synthesis of 3-(2-propylcarbonylaminopyridin-5-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound (338 mg, yield; 40%) from 5-bromo-2-propylcarbonylaminopyridine (3.11 g) and 3-

bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (514 mg). The resulting free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 168-171°C

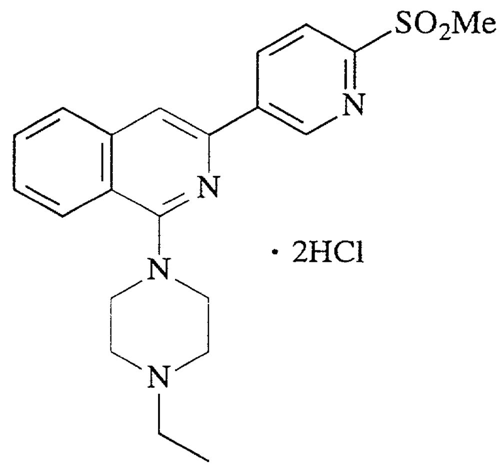
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.94(t,J=7.2Hz,3H), 1.35(t,J=7.2Hz,3H), 1.66(q,J=7.2Hz,2H), 2.47(t,J=7.2Hz,2H), 3.18-3.26(m,2H), 3.30-3.40(m,2H), 3.54-3.63(m,4H), 4.02(d,J=14.0Hz,2H), 7.64(t,J=8.0Hz,1H), 7.78(t,J=8.0Hz,1H), 7.99(d,J=8.0Hz,1H), 8.13,(d,J=8.8Hz,1H), 8.16(s,1H), 8.16(d,J=8.0Hz,1H), 8.69(dd,J=8.8,2.4Hz,1H), 9.14(d,J=2.4Hz,1H).

MS(FAB) m/z 404$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.04(t,J=7.2Hz,3H), 1.17(t,J=7.2Hz,3H), 1.76-1.85(m,2H), 2.42(t,J=7.2Hz,2H), 2.60(q,J=7.2Hz,2H), 2.76(br,4H), 3.56(br,4H), 7.48(ddd,J=8.4,8.0,1.2Hz,1H), 7.61(ddd,J=8.4,8.0,1.2Hz,1H), 7.65(s,1H), 7.79(d,J=8.4Hz,1H), 8.07(d,J=8.4Hz,1H), 8.31(d,J=8.8Hz,1H), 8.44(dd,J=8.8,2.4Hz,1H), 9.06(br,1H).

Example 129 Synthesis of 3-[(2-methylsulfonylpyridin)-5-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound (609 mg, yield; 82%) from 5-bromo-2-methylsulfonylpyridine (1.72 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (582 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 248-250°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 3.20-3.26(m,2H), 3.35(s,3H), 3.30-3.40(m,2H), 3.56-3.63(m,4H), 4.00(d,J=14.0Hz,2H), 7.71(t,J=8.0Hz,1H), 7.82(t,J=8.0Hz,1H), 8.05(d,J=8.0Hz,1H), 8.17(d,J=8.0Hz,1H), 8.18(d,J=8.0Hz,1H), 8.37(s,1H), 8.86(dd,J=8.0,2.4Hz,1H), 9.57(d,J=2.4Hz,1H).

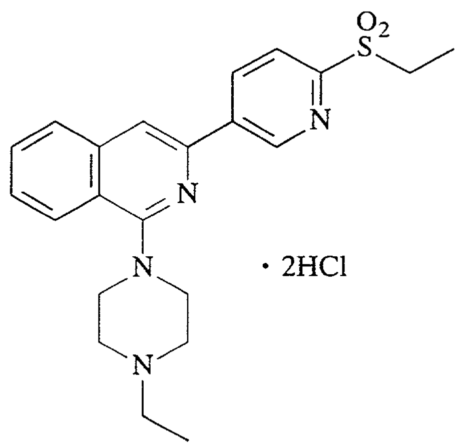
MS(FAB) m/z 397(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.76(t,J=4.8Hz,4H), 3.28(s,3H),

3.61(t,J=4.8Hz,4H), 7.56(t,J=8.0Hz,1H), 7.67(t,J=8.0Hz,1H), 7.79(s,1H), 7.85(d,J=8.0Hz,1H), 8.11(d,J=8.0Hz,1H), 8.17(d,J=8.0Hz,1H), 8.67(dd,J=8.0,2.0Hz,1H), 9.48(d,J=2.0Hz,1H).

Example 130 Synthesis of 3-[(2-ethylsulfonylpyridin)-5-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (710 mg, yield; 96%) from 5-bromo-2-ethylsulfonylpyridine (1.77 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (579 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 155-159°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.35(t,J=7.2Hz,3H), 3.19-3.26(m,2H), 3.32-3.40(m,2H), 3.50(q,J=7.2Hz,2H), 3.59-3.66(m,4H), 4.07(d,J=13.2Hz,2H), 7.71(t,J=8.0Hz,1H), 7.83(t,J=8.0Hz,1H), 8.04(d,J=8.0Hz,1H),

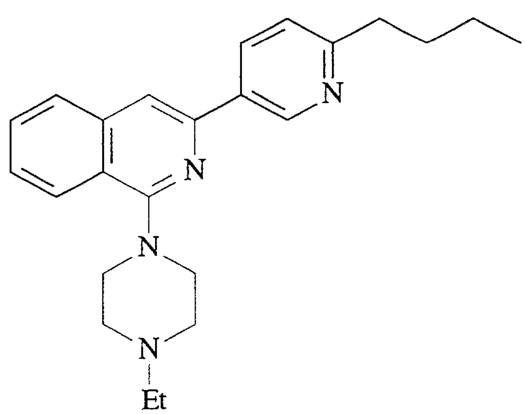
8.17(d,J=8.0Hz,1H), 8.19(d,J=8.4Hz,1H), 8.38(s,1H), 8.87(dd,J=8.4,2.0Hz,1H), 9.58(d,J=2.0Hz,1H).

MS(FAB) m/z 411$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.34(t,J=7.6Hz,3H), 2.56(q,J=7.2Hz,2H), 2.76(t,J=4.8Hz,4H), 3.45(q,J=7.6Hz,2H), 3.61(t,J=4.8Hz,4H), 7.56(ddd,J=8.4,8.0,1.2Hz,2H), 7.66(ddd,J=8.4,8.0,1.2Hz,1H), 7.79(s,1H), 7.85(d,J=8.0Hz,1H), 8.11(d,J=8.4Hz,1H), 8.17(d,J=8.4Hz,1H), 8.67(dd,J=8.4,2.0Hz,1H), 9.49(d,J=2.0Hz,1H).

Example 131 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(2-butylpyridin-5-yl)isoquinoline



1-(1-Ethylpiperazin-4-yl)-3-[2-(1-butyn-1-yl)pyridin-5-yl]isoquinoline (148 mg) was dissolved in ethanol (20 ml), followed by the addition of platinum oxide (15 mg), and the mixture was stirred in hydrogen atmosphere at room temperature overnight. After the platinum oxide was filtered off, the resulting solution was evaporated, and the resulting residue

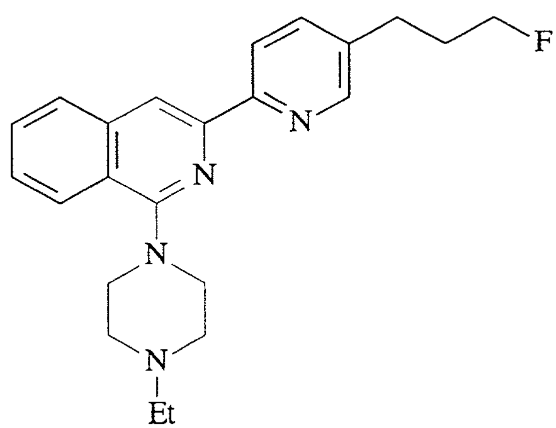
was purified by (NH) silica gel column chromatography (ethyl acetate/hexane system). Continuously, the resulting product was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as a pale brown amorphous (98 mg, yield; 50%).

Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.90(3H,t,J=7.2Hz), 1.24(3H,t,J=7.2Hz), 1.27-1.38(2H,m), 1.64-1.72(2H,m), 2.78(2H,t,J=7.6Hz), 3.12(2H,q,J=7.2Hz), 3.32-3.42(4H,brs), 7.36(1H,d,J=8Hz), 7.61(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.74(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.96(1H,d,J=8Hz), 8.10(1H,s), 8.11(1H,d,J=8Hz), 8.40(1H,dd,J=8Hz,2.4Hz), 9.25(1H,d,J=2.4Hz).

ESI-Mass; 375(MH$^+$).

Example 132 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[5-(3-fluoropropyl)pyridin-2-yl)isoquinoline



Diethylaminosulfur trifluoride (237 ml) was dissolved in methylene chloride (2 ml), followed by the addition of 1-(1-ethylpiperazin-4-yl)-3-[5-(3-hydroxypropyl)pyridin-2-

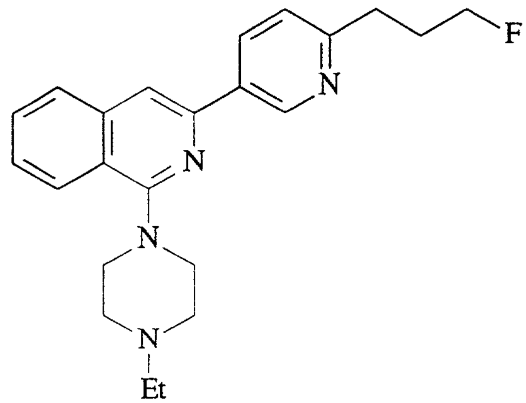
yl]isoquinoline (160 mg)/methylene chloride (2 ml) solution in nitrogen atmosphere at -70 °C. After the cooling bath was removed, subsequently, the resulting mixture was stirred for 2 hr. The reaction solution was diluted with methylene chloride, washed subsequently with an aqueous solution of saturated sodium bicarbonate and brine, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by (NH) silica gel column chromatography (ethyl acetate/hexane system), to give the oxalate of the title compound as a yellow amorphous (60 mg, yield; 31%).

Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.26(3H,t,J=7.2Hz), 1.94-2.10(2H,m), 2.76(2H,t,J=7.6Hz), 3.17(2H,q,J=7.2Hz), 3.35-3.48(4H,m), 3.60-3.80(4H,m), 4.43(1H,t,J=6Hz), 4.55(1H,t,J=6Hz), 7.62(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.73(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.82(1H,dd,J=8Hz,2.4Hz), 8.07(1H,d,J=8Hz), 8.13(1H,d,J=8Hz), 8.34(1H,d,J=8Hz), 8.45(1H,s), 8.55(1H,d,J=2.4Hz).

ESI-Mass; 379(MH^+).

Example 133 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(3-fluoropropyl)pyridin-5-yl]isoquinoline



Diethylaminosulfur trifluoride (53 ml) and pyridine hydrogen fluoride (320 ml) were dissolved in methylene chloride (3 ml), followed by the addition of 1-(1-ethylpiperazin-4-yl)-3-[5-(3-hydroxypropyl)pyridin-2-yl]isoquinoline (152 mg)/methylene chloride (2 ml) solution in nitrogen atmosphere at -70 °C. After the cooling bath was removed, subsequently, the resulting mixture was stirred for 2 hr. The reaction solution was diluted with methylene chloride, washed sequentially with an aqueous solution of sodium bicarbonate and brine, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by (NH) silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a yellow oil (6 mg, yield; 5%).

Free compound:

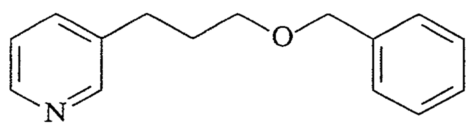
^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(3H,t,J=7.2Hz), 2.15-2.28(2H,m), 2.56(2H,q,J=7.2Hz), 2.76(4H,t,J=4.4Hz), 2.99(2H,t,J=7.6Hz), 3.60(4H,t,J=6.4Hz), 4.48(1H,t,J=6.4Hz), 4.60(1H,t,J=6.4Hz), 7.28(1H,d,J=8Hz), 7.49(1H,dd,J=8Hz,7Hz), 7.61(1H,dd,J=8Hz,7Hz), 7.68(1H,s), 7.81(1H,d,J=8Hz),

8.09(1H,d,J=8Hz), 8.35(1H,dd,J=8Hz,2.4Hz), 9.30(1H,d,J=2.4Hz).

ESI-Mass; 379(MH^+).

Example 134 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[5-(3-hydroxypropyl)pyridin-2-yl]isoquinoline

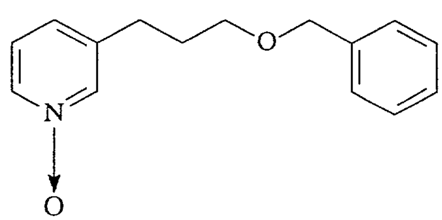
(134-1) 3-(3-Benzyloxypropyl)pyridine



In the same manner as in Example 167-1, the title compound was obtained as a brown oil (34.28 g, yield; 83%) from 3-pyridinepropanol (24.882 g) and benzyl bromide (26 ml).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.90-1.97(2H,m), 2.73(2H,t,J=7.8Hz), 3.48(2H,t,J=6.4Hz), 4.50(2H,s), 7.18(1H,dd,J=8Hz,4.8Hz), 7.27-7.37(5H,m), 7.48(1H,ddd,J=8Hz,2.4Hz,1.6Hz), 8.43(1H,dd,J=4.8Hz,1.6Hz), 8.45(1H,d,J=2.4Hz).

(134-2) 3-(3-Benzyloxypropyl)pyridine N-oxide

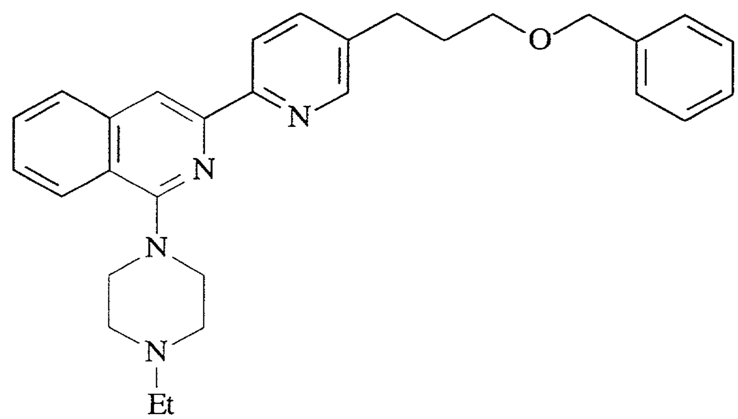


3-(3-Benzyloxypropyl)pyridine (34.28 g) was dissolved in acetic acid (260 ml), followed by the addition of a 30 % aqueous solution of hydrogen peroxide (52 ml), and the mixture was stirred at 50°C overnight. After cooling as it was, water (52

ml) was added to the reaction solution, which was then evaporated. The resulting residue was dissolved in chloroform, washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the title compound as a yellow oil (30.23 g, yield; 88%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.87-1.95(2H,m), 2.70(2H,t,J=7.8Hz), 3.47(2H,t,J=6Hz), 4.50(2H,s), 7.08(1H,d,J=8Hz), 7.16(1H,dd,J=8Hz,6.4Hz), 7.28-7.39(5H,m), 8.05-8.10(2H,m).

(134-3) 1-(1-Ethylpiperazin-4-yl)-[5-(3-benzyloxypropyl)pyridin-2-yl]isoquinoline

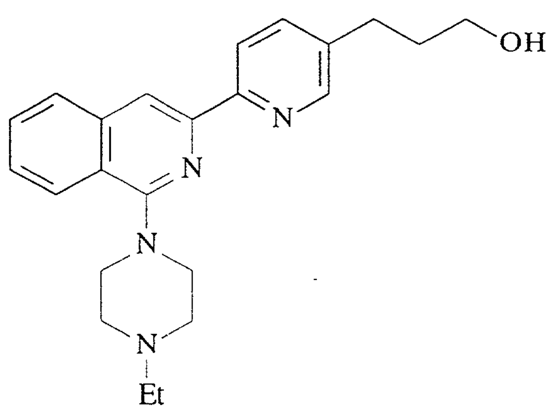


3-(3-Benzyloxypropyl)pyridine N-oxide (4.546 g) was dissolved in methylene chloride, phosphorus oxybromide (11.47 g) was added thereto under ice-cooling, and the mixture was stirred for 2 hr. Then, it was further stirred at room temperature for 2 hr. The reaction mixture was poured into warm water, and then it was neutralized by adding sodium bicarbonate thereto. The mixture was extracted with ethyl acetate. The

resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give a mixture of 2-bromo-5-(3-benzyloxypropyl)pyridine and 2-bromo-3-(3-benzyloxypropyl)pyridine (1:1) as a brown oil (2.203 g). The resulting mixture (1.111 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (662 mg) were treated in the same manner as in Example 167-2, to give the title compound as a yellow oil (326 mg, yield; 33%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(3H,t,J=7.2Hz), 1.94-2.02(2H,m), 2.56(2H,q,J=7.2Hz), 2.77(4H,t,J=4Hz), 2.80(2H,t,J=7.2Hz), 2.80(2H,t,J=7.2Hz), 3.52(2H,t,J=6Hz), 3.59(4H,t,J=4Hz), 4.52(2H,s), 7.27-7.37(5H,m), 7.49(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.60(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.62(1H,dd,J=8.4Hz,2.4Hz), 7.88(1H,d,J=8Hz), 8.10(1H,d,J=8Hz), 8.36(1H,s), 8.43(1H,dd,J=8.4Hz), 8.52(1H,d,J=2.4Hz).

(134-4) 1-(1-Ethylpiperazin-4-yl)-3-[5-(3-hydroxypropyl)pyridin-2-yl]isoquinoline



In the same manner as in Example 167-3, the oxalate of the title compound was obtained as a yellow amorphous (150 mg, yield; 43%) from 1-(1-ethylpiperazin-4-yl)-3-[5-(3-benzyloxypropyl)pyridin-2-yl]isoquinoline (326 mg).

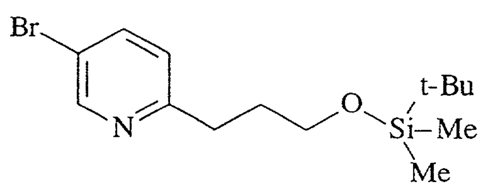
Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.24(3H,t,J=7.2Hz), 1.72-1.80(2H,m), 2.69(2H,t,J=7.8Hz), 3.11(2H,q,J=7.2Hz), 3.30-3.40(4H,m), 3.44(2H,t,J=6.2Hz), 7.62(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.73(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.78(1H,dd,J=8.4Hz,2.4Hz), 8.06(1H,d,J=8Hz), 8.12(1H,d,J=8.4Hz), 8.33(1H,d,J=8Hz), 8.43(1H,s), 8.53(1H,d,J=2.4Hz).

ESI-Mass; 377(MH^+).

Example 135 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(3-hydroxypropyl)pyridin-5-yl]isoquinoline

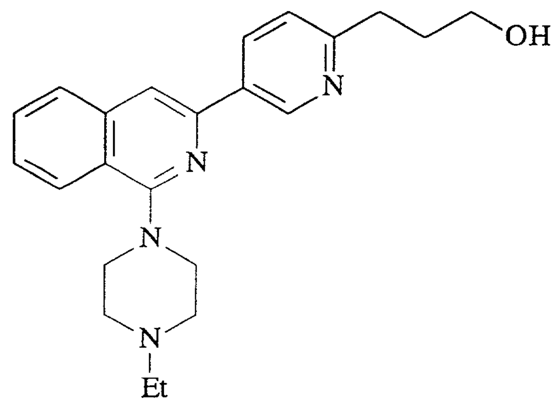
(135-1) 5-Bromo-2-[3-(t-butyldimethylsilyloxy)propyl]pyridine



From 5-bromo-2-pyridinepropanol (4.266 g) synthesized according to J. O. C., 53, 386, 1988, the title compound was obtained as a colorless oil in the same manner as in Example 163-1 (6.297 g, yield; 97%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.04(6H,s), 0.90(9H,s), 1.89-1.97(2H,m), 2.82(2H,t,J=7.8Hz), 3.65(2H,t,J=6.2Hz), 7.07(1H,dd,J=8Hz,2.4Hz), 8.57(1H,d,J=2.4Hz).

(135-2) 1-(1-Ethylpiperazin-4-yl)-3-[2-(3-hydroxypropyl)pyridin-5-yl]isoquinoline



In the same manner as in Example 167-2, the free compound of the title compound was obtained as a yellow solid (1.288 g, yield; 94%) from 5-bromo-2-[3-(t-butyl)dimethylsilyloxypropyl]pyridine (2.973 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (1.158 g). A part (150 mg) of the resulting free compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as a pale yellow amorphous (80 mg, yield; 43%).

Oxalate:

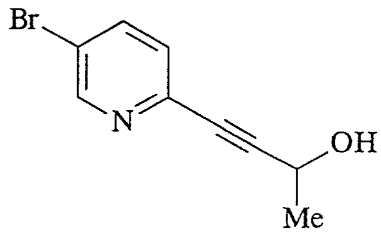
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.25(3H,t,J=7.2Hz), 1.80-1.84(2H,m), 2.81(2H,t,J=7.6Hz), 3.15(2H,q,J=7.2Hz), 3.34-3.46(4H,m), 3.45(2H,t,J=6.4Hz), 3.60-3.80(4H,m), 7.61(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.74(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.96(1H,d,J=8Hz), 8.11(1H,s), 8.11(1H,d,J=8Hz), 8.40(1H,dd,J=8Hz,2.4Hz), 9.26(1H,d,J=2.4Hz).

ESI-Mass ; 377 (MH$^+$).

Example 136 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(3-

hydroxybutyl)pyridin-5-yl]isoquinoline

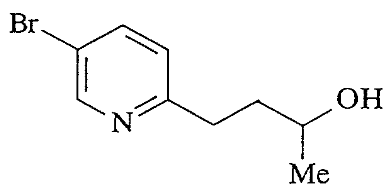
(136-1) 5-Bromo-2-(3-hydroxy-1-butynyl)pyridine



In the same manner as in Example 139-1, the title compound was obtained as a brown solid (15.895 g, yield; 88%) from 2,5-dibromopyridine (18.951 g) and 3-butyn-2-ol (6.3 ml).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.57(3H,d,J=6.8Hz), 4.77(1H,m), 7.31(1H,d,J=7.8Hz), 7.79(1H,dd,J=7.8Hz,2.4Hz), 8.63(1H,d,J=2.4Hz).

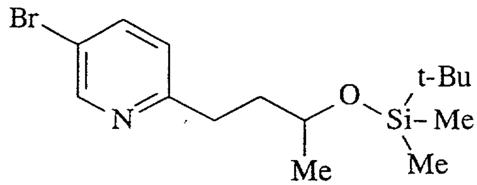
(136-2) 5-Bromo-2-(3-hydroxybutyl)pyridine



In the same manner as in Example 139-2, the title compound was obtained as a yellow oil (2.783 g, yield; 60%) from 5-bromo-2-(3-hydroxy-1-butyryl)pyridine (4.521 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.23(3H,d,J=6Hz), 1.78-1.93(2H,m), 2.91(2H,t,J=7.8Hz), 3.23(1H,br-s), 3.78-3.88(1H,m), 7.09(1H,d,J=8.4Hz), 7.73(1H,dd,J=8.4Hz,2.4Hz), 8.55(1H,d,J=2.4Hz).

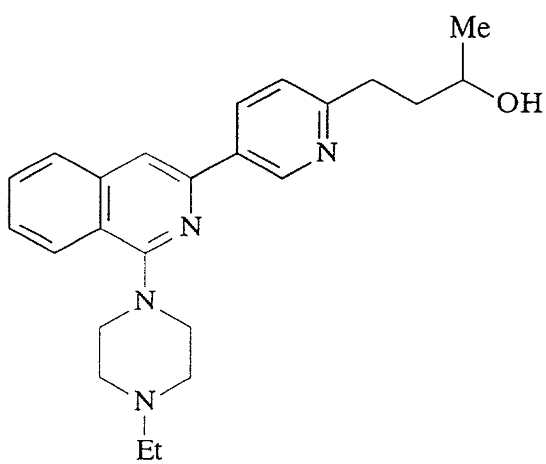
(136-3) 5-Bromo-2-[3-(t-butyldimethylsilyloxy)butyl]pyridine



In the same manner as in Example 163-1, the title compound was obtained as a colorless oil (3.75 g, yield; 95%) from 5-bromo-2-(3-hydroxybutyl)pyridine (2.647 g).

^{1}H-NMR(400MHz, $CDCl_3$); δ (ppm) 0.04(6H,s), 0.88(9H,s), 1.16(3H,d,J=6Hz), 1.77-1.83(2H,m), 2.67-2.87(2H,m), 3.56-3.58(1H,m), 7.04(1H,d,J=8.4Hz), 7.69(1H,J=8.4Hz,2.4Hz), 8.55(1H,d,J=2.4Hz).

(136-4) 1-(1-Ethylpiperazin-4-yl)-3-[2-(3-hydroxybutyl)pyridin-5-yl]isoquinoline



In the same manner as in Example 167-2, the oxalate of the title compound was obtained as a yellow amorphous (420 mg, yield; 56%) from 5-bromo-2-[3-(t-butyl)dimethylsilyloxybutyl]pyridine (2.066 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (491 mg).

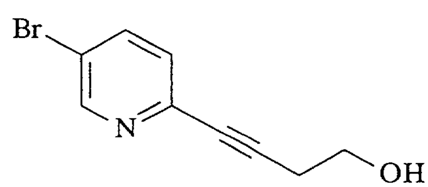
Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.09(3H,d,J=6Hz), 1.24(3H,t,J=7.2Hz), 1.70-1.78(2H,m), 2.74-2.90(2H,m), 3.13(2H,q,J=7.2Hz), 3.37(4H,br-s), 3.60-3.76(6H,m), 7.37(2H,d,J=8.4Hz), 7.61(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.74(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.96(1H,d,J=8Hz), 8.10(1H,s), 8.11(1H,d,J=8Hz), 8.39(1H,dd,J=8.4Hz,2.4Hz), 9.25(1H,d,J=2.4Hz).

ESI-Mass; 391(MH^+).

Example 137 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(4-hydroxybutyl)pyridin-5-yl]isoquinoline

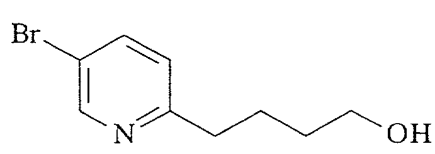
(137-1) 5-Bromo-2-(4-hydroxy-1-butynyl)pyridine



In the same manner as in Example 139-1, the title compound was obtained as a brown solid (6.6 g, yield; 48%) from 2,5-dibromopyridine (14.213 g) and 3-butyn-1-ol (4.5 ml).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 2.72(2H,t,J=6.4Hz), 3.85(1H,t,J=6.4Hz), 3.86(1H,t,J=6.4Hz), 7.29(1H,d,J=8.4Hz), 7.77(1H,dd,J=8.4Hz,2.4Hz), 8.60(1H,d,J=2.4Hz).

(137-2) 5-Bromo-2-(4-hydroxybutyl)pyridine

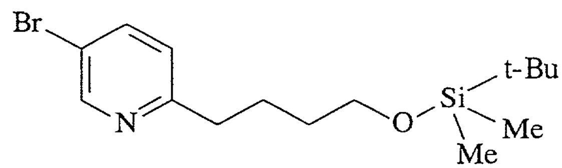


In the same manner as in Example 139-2, the title compound was obtained as a yellow oil (3.397 g, yield; 74%) from 5-

bromo-2-(4-hydroxy-1-butynyl)pyridine (4.522 g).

[1]H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.61-1.67(2H,m), 1.77-1.85(3H,m), 2.80(2H,t,J=7.6Hz), 3.68(2H,m), 7.07(1H,d,J=8Hz), 7.72(1H,dd,J=8Hz,2.4Hz), 8.57(1H,d,J=2.4Hz).

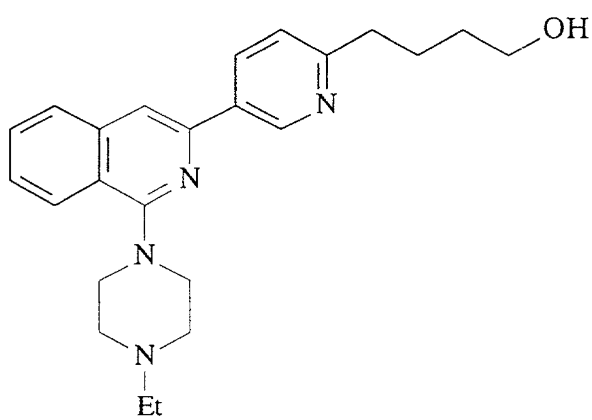
(137-3) 5-Bromo-2-[4-(t-butyldimethylsilyloxy)butyl]pyridine



In the same manner as in Example 163-1, the title compound was obtained as a colorless oil (2.484 g, yield; 87%) from 5-bromo-2-(4-hydroxybutyl)pyridine (1.905 g).

[1]H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.04(6H,s), 0.88(9H,s), 1.52-1.60(2H,m), 1.72-1.79(2H,m), 2.76(2H,t,J=7.6Hz), 3.63(2H,t,J=6.6Hz), 7.06(1H,d,J=8Hz), 7.70(1H,dd,J=8Hz,2.4Hz), 8.57(1H,d,J=2.4Hz).

(137-4) Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(4-hydroxybutyl)pyridin-5-yl]isoquinoline



In the same manner as in Example 167-2, the oxalate of the

title compound was obtained as a yellow amorphous (420 mg, yield; 64%) from 5-bromo-2-[4-(t-butyl)dimethylsilyloxybutyl]pyridine (2.484 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (435 mg).

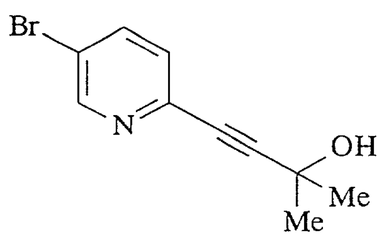
Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.25(3H,t,J=7.2Hz), 1.42-1.49(2H,m), 1.68-1.76(2H,m), 2.78(2H,t,J=7.6Hz), 3.15(2H,q,J=7.2Hz), 3.36-3.44(4H,br-s), 3.41(2H,t,J=6.2Hz), 7.36(1H,d,J=8Hz), 7.61(1H,dd,J=8Hz,7Hz), 7.74(1H,dd,J=8Hz,7Hz), 7.96(1H,d,J=8Hz), 8.11(1H,d,J=8Hz), 8.40(1H,dd,J=8Hz,2.4Hz), 9.26(1H,d,J=2.4Hz).

ESI-Mass; 391(MH^+).

Example 138 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(3-hydroxy-3-methylbutyl)pyridin-5-yl]isoquinoline oxalate

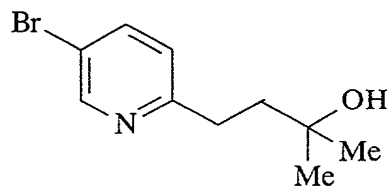
(138-1) 5-Bromo-2-(3-methyl-3-hydroxy-1-butynyl)pyridine



In the same manner as in Example 139-1, the title compound was obtained as a yellowish brown solid (17.91 g, yield; 94%) from 2,5-dibromopyridine (18.951 g) and 2-methyl-3-butyn-2-ol (6.3 ml).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.64(6H,s), 2.16(1H,br-s), 7.31(1H,d,J=8.4Hz), 7.78(1H,dd,J=8.4Hz,2.4Hz), 8.63(1H,d,J=2.4Hz).

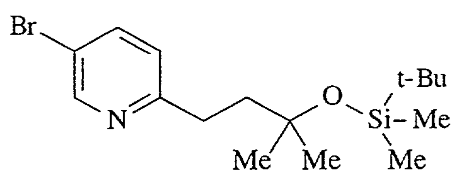
(138-2) 5-Bromo-2-(3-methylbutane-3-hydroxybutyl)pyridine



In the same manner as in Example 139-2, the title compound was obtained as a yellow oil (1.366 g, yield; 28%) from 5-bromo-2-(3-methyl-3-hydroxy-1-butynyl)pyridine (4.802 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.29(6H,s), 1.73(1H,s), 1.90(2H,t,J=7.8Hz), 7.09(1H,d,J=8.4Hz), 7.71(1H,dd,J=8.4Hz,2.4Hz), 8.55(1H,d,J=2.4Hz).

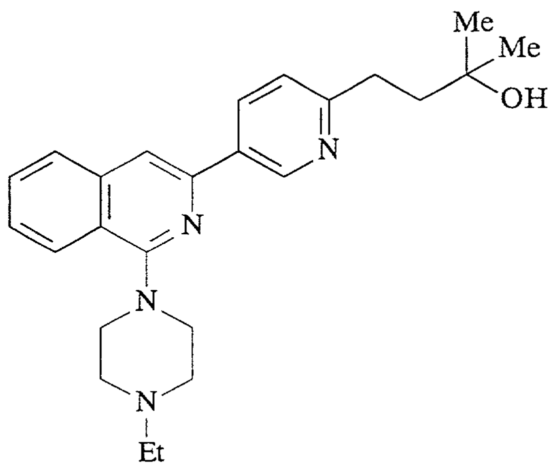
(138-3) 5-Bromo-2-[3-(t-butyldimethylsilyloxy)-3-methylbutyl]pyridine



5-Bromo-2-(3-methylbutane-3-hydroxybutyl)pyridine (1.359 g) was dissolved in methylene chloride (20 ml), followed by the sequential addition of 2,6-lutidine (2.5 ml) and t-butyldimethylsilyltrifluoromethanesulfonic acid (1.7 ml) in nitrogen atmosphere under ice-cooling, and the mixture was stirred overnight. The reaction mixture was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a colorless oil (1.724 g, yield; 86%).

^{1}H-NMR(400MHz, $CDCl_3$); δ (ppm) 0.10(6H,s), 0.88(9H,s), 1.27(6H,s), 1.78-1.83(2H,m), 2.82-2.87(2H,m), 7.06(1H,d,J=8.4Hz), 7.69(1H,dd,J=8.4Hz,2.4Hz), 8.56(1H,d,J=2.4Hz).

(138-4) 1-(1-Ethylpiperazin-4-yl)-3-[2-(3-hydroxy-3-methylbutyl)pyridin-5-yl]isoquinoline oxalate



In the same manner as in Example 167-2, the oxalate of the title compound was obtained as a yellow amorphous (132 mg, yield; 30%) from 5-bromo-2-[3-(t-butyl)dimethylsilyloxy-3-methylbutyl]pyridine (1.724 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (324 mg).

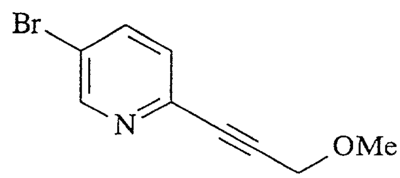
Oxalate:

^{1}H-NMR(400MHz, DMSO-d_6); δ (ppm) 1.15(6H,s), 1.25(3H,t,J=7.2Hz), 1.74-1.79(2H,m), 2.80-2.85(2H,m), 3.13(2H,q,J=7.2Hz), 3.32-3.42(4H,br-s), 3.58-3.78(4H,br-s), 7.37(1H,d,J=8Hz), 7.61(1H,dd,J=8Hz,7Hz), 7.74(1H,dd,J=8Hz,7Hz), 7.96(1H,d,J=8Hz), 8.10(1H,s), 8.11(1H,d,J=8Hz), 8.40(1H,dd,J=8Hz,2.4Hz), 9.25(1H,d,J=2.4Hz).

ESI-Mass; 405(MH^+).

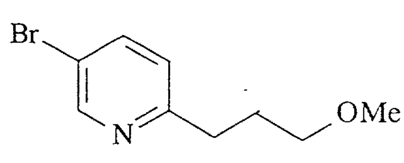
Example 139 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(3-methoxypropyl)pyridin-5-yl]isoquinoline oxalate

(139-1) 5-Bromo-2-(3-methoxypropynyl)pyridine



2,5-Dibromopyridine (16.582 g) was dissolved in triethylamine (200 ml), followed by the addition of methyl propargyl ether (5.9 ml), copper iodide (267 mg) and bis(triphenylphosphine)palladium (II) chloride (46 mg). The resulting mixture was stirred in nitrogen atmosphere at room temperature for 1 hr. Subsequently, it was stirred at room temperature for further 3 hr. After the resulting insoluble matters were filtered off, the resulting solution was evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a brown solid (12.411 g, yield; 79%).
^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 3.47(3H,d,J=0.8Hz), 4.34(2H,s), 7.34(1H,d,J=8Hz), 7.79(1H,ddd,J=8Hz,2.4Hz,0.8Hz), 8.64(1H,d,J=2.4Hz).

(139-2) 5-Bromo-2-(3-methoxypropyl)pyridine

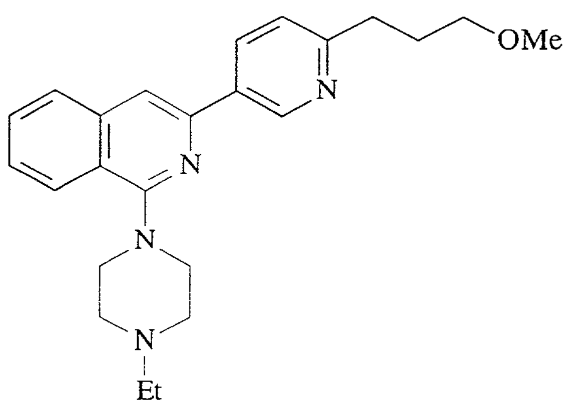


5-Bromo-2-(3-methoxypropynyl)pyridine (5.652 g) was

dissolved in ethanol (150 ml), followed by the addition of triethylamine (2.5 ml) and platinum oxide (230 mg), and the resulting mixture was stirred in hydrogen atmosphere at room temperature for 5 hr. After the platinum oxide was filtered off, the resulting mixture was evaporated and partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a yellow oil (3.991 g, yield; 68%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.95-2.03(2H,m), 2.82(2H,t,J=7.6Hz), 3.34(3H,s), 3.41(2H,t,J=6.4Hz), 7.07(1H,d,J=8Hz), 7.71(1H,dd,J=8Hz,2.4Hz), 8.58(1H,d,J=2.4Hz).

<u>(139-3) Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(3-methoxypropyl)pyridin-5-yl]isoquinoline oxalate</u>



In the same manner as in Example 167-2, the oxalate of the title compound was obtained as a yellow amorphous (982 mg, yield; 74%) from 5-bromo-2-(3-methoxypropyl)pyridine (2.301

g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (865 mg).

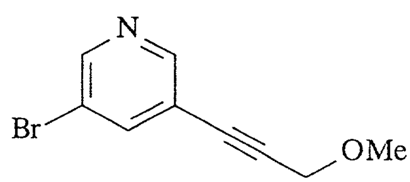
Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.24(3H,t,J=7.2Hz), 1.88-1.97(2H,m), 2.81(2H,t,J=7.6Hz), 3.13(2H,q,J=7.2Hz), 3.23(3H,s), 3.32-3.42(6H,m), 3.60-3.80(4H,m), 7.37(1H,d,J=8Hz), 7.61(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.74(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.96(1H,d,J=8Hz), 8.11(1H,d,J=8Hz), 8.11(1H,s), 8.40(1H,dd,J=8Hz,2.4Hz), 9.27(1H,d,J=2.4Hz).

ESI-Mass; 391(MH^+).

Example 140 Synthesis of 1-(1-Ethylpiperazin-4-yl)-3-[3-(3-methoxypropyl)pyridin-5-yl]isoquinoline oxalate

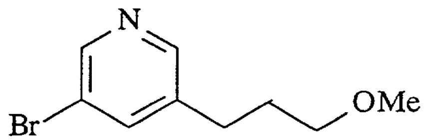
(140-1) 5-Bromo-3-(3-methoxypropynyl)pyridine



In the same manner as in Example 139-1, the title compound was obtained as a yellowish orange solid (7.216 g, yield; 64%) from 3,5-dibromopyridine (11.854 g) and methyl propargyl ether (4.2 ml).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 3.46(3H,s), 4.33(2H,s), 7.89(1H,t,J=2Hz), 8.58(1H,d,J=2Hz), 8.61(1H,d,J=2Hz).

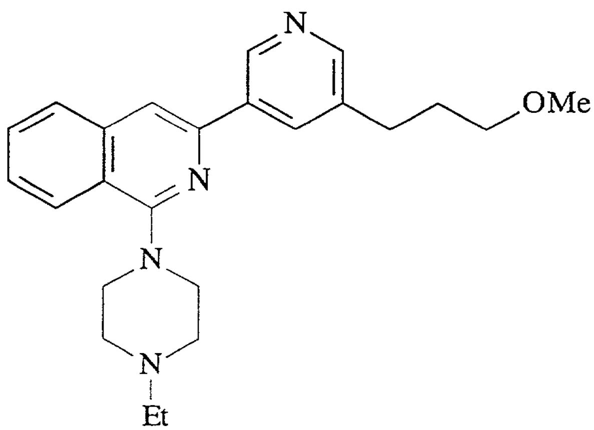
(140-2) 5-Bromo-3-(3-methoxypropyl)pyridine



In the same manner as in Example 139-2, the title compound was obtained as a pale yellow oil (3.62 g, yield; 79%) from 5-bromo-3-(3-methoxypropynyl)pyridine (4.521 g).

^{1}H-NMR(400MHz, $CDCl_3$); δ (ppm) 1.85-1.92(2H,m), 2.70(2H,t,J=7.8Hz), 3.35(3H,s), 3.38(2H,t,J=6.2Hz), 7.67(1H,t,J=2Hz), 8.37(1H,d,J=2Hz), 8.51(1H,d,J=2Hz).

(140-3) 1-(1-Ethylpiperazin-4-yl)-3-[3-(3-methoxypropyl)pyridin-5-yl]isoquinoline oxalate



In the same manner as in Example 167-2, the oxalate of the title compound was obtained as a yellow amorphous (324 mg, yield; 64%) from 5-bromo-3-(3-methoxypropyl)pyridine (1.151 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (345 mg).

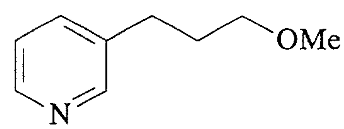
Oxalate:

^{1}H-NMR(400MHz, DMSO-d_6); δ (ppm) 1.25(3H,t,J=7.2Hz), 1.84-1.92(2H,m), 2.73(2H,t,J=7.6Hz), 3.16(2H,q,J=7.2Hz),

3.25(3H,s), 3.36(2H,t,6.4Hz), 3.38-3.48(4H,m), 3.60-3.80(4H,m), 7.63(1H,ddd,J=8.4Hz,7Hz,1.2Hz), 7.76(1H,ddd,J=8.4Hz,7Hz,1.2Hz), 7.98(1H,d,J=8.4Hz), 8.12(1H,d,J=8.4Hz), 8.17(1H,m), 8.33(1H,t,J=2.4Hz), 8.43(1H,t,J=2.4Hz), 8.45(1H,d,J=2.4Hz), 9.21(1H,d,J=2.4Hz).
ESI-Mass; 391(MH^+).

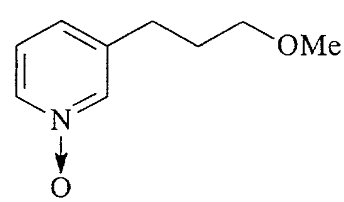
Example 141 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[5-(3-methoxypropyl)pyridin-2-yl]isoquinoline oxalate

(141-1) 3-(3-Methoxypropyl)pyridine



In the same manner as in Example 167-1, the title compound was obtained as a yellow oil (5.494 g, yield; 72%) from 3-pyridinepropanol (6.452 g) and methyl iodide (3.4 ml).
^1H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.86-1.93(2H,m), 2.70(2H,t,J=7.8Hz), 3.35(3H,s), 3.39(2H,t,J=6.2Hz), 7.21(1H,dd,J=8Hz,4.8Hz), 7.51(1H,dt,J=8Hz,1.6Hz), 8.45(1H,dd,J=4.8Hz,1.6Hz), 8.46(1H,d,J=1.6Hz).

(141-2) 3-(3-Methoxypropyl)pyridine N-oxide

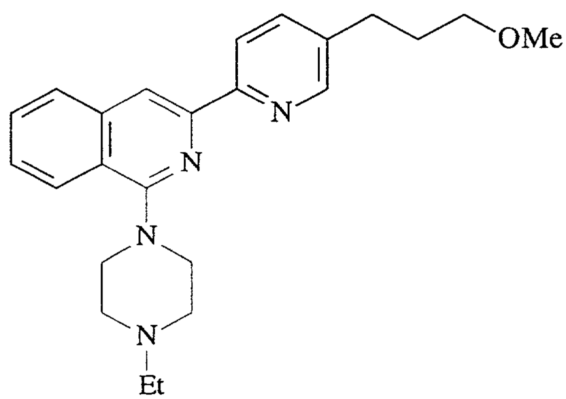


3-(3-Methoxypropyl)pyridine (5.551 g) was dissolved in methylene chloride (60 ml), followed by the addition of 70%

m-perbenzoic acid (10.86 g) and stirring under ice-cooling for 90 min. The reaction mixture was washed sequentially with a 10% aqueous solution of sodium sulfite and an aqueous solution of saturated sodium bicarbonate, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/methanol system), to give the title compound as a yellow oil (5.901 g, yield; 95%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.85-1.92(2H,m), 2.69(2H,t,J=7.6Hz), 3.35(3H,s), 3.39(2H,t,J=6.2Hz), 7.14(1H,d,J=7.2Hz), 7.21(1H,dd,J=7.2Hz,6.8Hz), 8.08-8.12(2H,m).

(141-3) 1-(1-Ethylpiperazin-4-yl)-3-[5-(3-methoxypropyl)pyridin-2-yl]isoquinoline oxalate



In the same manner as in Example 134-3, the oxalate of the title compound was obtained as a brown amorphous (120 mg, yield; 9%) from 3-(3-methoxypropyl)pyridine N-oxide (5.901 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (694 mg).

Oxalate:

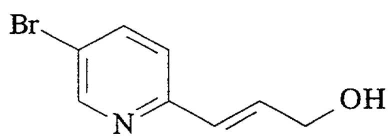
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.25(3H,t,J=7.2Hz), 1.80-

1.88(2H,m), 2.69(2H,t,J=7.2Hz), 3.15(2H,q,J=7.2Hz), 3.24(3H,s), 3.34(2H,t,J=6.2Hz), 3.34-3.46(4H,m), 3.58-3.80(4H,m), 7.26(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.74(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.78(1H,dd,J=8.4Hz,2.4Hz,), 8.07(1H,d,J=8Hz), 8.13(1H,d,J=8Hz), 8.33(1H,d,J=8.4Hz), 8.44(1H,s), 8.53(1H,d,J=2.4Hz).

ESI-Mass; 391(MH^+).

Example 142 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(3-ethoxypropyl)pyridin-5-yl]isoquinoline oxalate

(142-1) 5-Bromo-2-(3-hydroxy-1-propenyl)pyridine

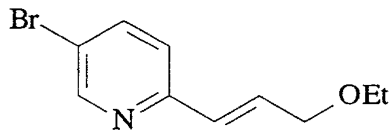


3-(5-Bromo-2-pyridinyl)-3-propyn-1-ol (10.602 g) synthesized according to J. O. C., 53, 386, 1988 was dissolved in tetrahydrofuran (100 ml), to which were then added lithium aluminum hydride (1.06 g) in several portions under ice-cooling, and then the mixture was stirred for 10 min. Water (1.1 ml), 5N sodium hydroxide (1.1 ml) and water (3.3 ml) were sequentially added to the reaction mixture, and the resulting insoluble matters were filtered off through Celite. The resulting filtrate was evaporated, and the resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a colorless solid (3.718 g, yield; 34%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 2.66(1H,br-s), 4.38(2H,br-s),

6.68(1H,dt,J=15.6Hz,5Hz), 7.18(1H,d,8.4Hz), 7.74(1H,dd,J=8.4Hz,2.4Hz), 8.58(1H,d,J=2.4Hz).

(142-2) 5-Bromo-2-(3-ethoxy-1-propenyl)pyridine

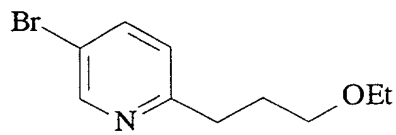


5-Bromo-2-(3-hydroxy-1-propenyl)pyridine (3.718 g) was dissolved in tetrahydrofuran (60 ml), followed by the sequential addition of triethylamine (7.1 ml) and methanesulfonyl chloride (1.6 ml) under ice-cooling, and the resulting mixture was stirred as it was, for 25 min. After the resulting insoluble matters were filtered off, the mixture was evaporated. The resulting residue was dissolved in ethanol (60 ml), followed by the addition of sodium ethoxide (1.388 g)/ethanol (25 ml) solution under ice-cooling, and the mixture was stirred at room temperature for 3.5 hr. The reaction mixture was evaporated, and the resulting residue was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a yellow oil (2.607 mg, yield; 65%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.25(3H,t,J=7.2Hz), 3.56(2H,q,J=7.2Hz), 4.17(2H,dd,J=5.2Hz,1.6Hz), 6.65(1H,dt,J=15.8Hz,1.6Hz), 6.79(1H,dt,J=15.8Hz,5.2Hz), 7.16(1H,d,J=8.4Hz), 7.71(1H,dd,J=8.4Hz,2.4Hz),

8.58(1H,d,J=2.4Hz).

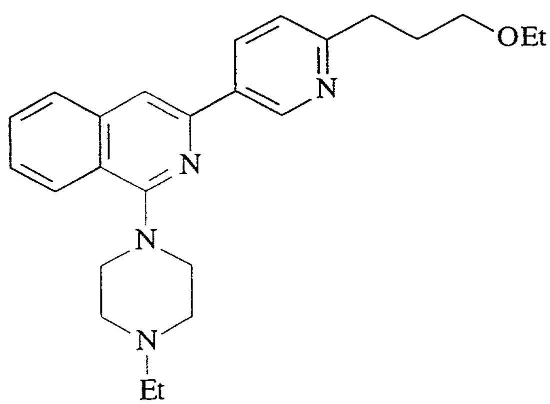
(142-3) 5-Bromo-2-(3-ethoxypropyl)pyridine



The title compound was obtained as a brown oil (2.286 g, yield; 74%) from 5-bromo-2-(3-ethoxy-1-propenyl)pyridine (3.079 g) in the same manner as in Example 139-2.

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.19(3H,t,J=7.2Hz), 1.96-2.03(2H,m), 2.83(2H,t,J=7.8Hz), 3.45(2H,t,J=6Hz), 3.47(2H,q,J=7.2Hz), 7.08(1H,d,J=8.4Hz), 7.70(1H,dd,J=8.4Hz,2.4Hz), 8.58(1H,d,J=2.4Hz).

(142-4) 1-(1-Ethylpiperazin-4-yl)-3-[2-(3-ethoxypropyl)pyridin-5-yl]isoquinoline oxalate



In the same manner as in Example 167-2, the oxalate of the title compound was obtained as a pale yellow amorphous (472 mg, yield; 91%) from 5-bromo-2-(3-ethoxypropyl)pyridine (1.465 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (348 mg).

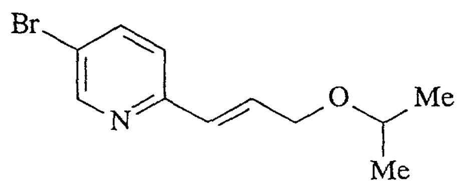
Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.10(3H,t,J=7.2Hz), 1.25(3H.t,J=7.2Hz), 1.88-1.96(2H,m), 2.82(2H,t,J=7.6Hz), 3.13(2H,q,J=7.2Hz), 3.36-3.43(8H,m), 3.58-3.80(4H,br-s), 7.37(1H,d,J=8Hz), 7.61(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.74(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.96(1H,d,J=8Hz), 8.11(1H,s), 8.11(1H,d,J=8Hz), 8.41(1H,dd,,J=8Hz,2.4Hz), 9.27(1H,d,J=2.4Hz).

ESI-Mass; 405(MH$^+$).

Example 143 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-[3-(2-propoxy)propyl]pyridin-5-yl]isoquinoline oxalate

(143-1) 5-Bromo-2-[3-(2-propoxy)-1-propenyl]pyridine

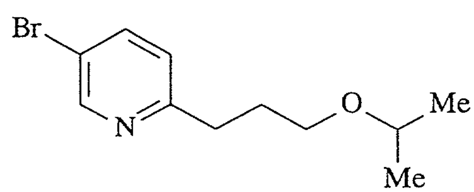


5-Bromo-2-(3-hydroxy-1-propenyl)pyridine (8.891 g) was dissolved in tetrahydrofuran (200 ml), followed by the sequential addition of triethylamine (17.6 ml) and methanesulfonyl chloride (3.9 ml) under ice-cooling, and the mixture was stirred for 20 min. After the resulting insoluble matters were filtered off, the solution was evaporated. The resulting residue was dissolved in 2-propanol (100 ml), sodium 2-propanoxide/2-propanol solution prepared from 60% sodium hydride (2 g) and 2-propanol (70 ml) was added thereto under ice-cooling, and the resulting mixture was stirred, as it was, at room temperature for 30 min. After the resulting insoluble

matters were filtered off from the reaction mixture, the resulting solution was evaporated and partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a brown oil (3.519 g, yield; 33%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.22(6H,d,J=6Hz), 3.69(1H,sept,J=6Hz), 4.18(2H,dd,J=5.2Hz,1.6Hz), 6.66(1H,dd,J=15.8Hz,1.6Hz), 6.79(1H,dd,J=15.8Hz,5.2Hz), 7.19(1H,d,J=8.4Hz), 7.73(1H,dd,J=8.4Hz,2.4Hz), 8.59(1H,d,J=2.4Hz).

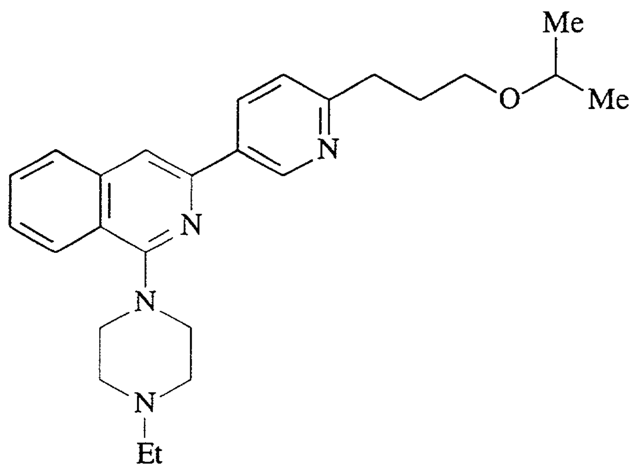
(143-2) 5-Bromo-2-[3-(2-propoxy)propyl]pyridine



In the same manner as in Example 139-2, the title compound was obtained as a yellow oil (2.859 g, yield; 81%) from 5-bromo-2-[3-(2-propoxy)-1-propenyl]pyridine (3.519 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.14(6H,d,J=6Hz), 1.94-2.01(2H,m), 2.83(2H,t,J=7.8Hz), 3.43(2H,t,J=6Hz), 3.54(1H,sept,J=6Hz), 7.08(1H,d,J=8.4Hz), 7.70(1H,dd,J=8.4Hz,2.4Hz), 8.57(1H,d,2.4Hz).

(143-3) 1-(1-Ethylpiperazin-4-yl)-3-[2-[3-(2-propoxy)propyl]pyridin-5-yl]isoquinoline oxalate



In the same manner as in Example 167-2, the oxalate of the title compound was obtained as a pale yellow amorphous (418 mg. yield; 73%) from 5-bromo-2-[3-(2-propoxy)propyl]pyridine (1.291 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (348 mg).

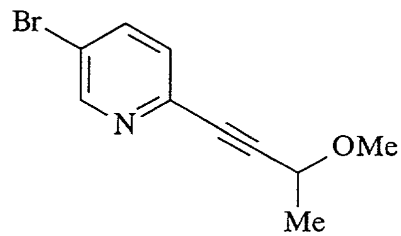
Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.07(3H,t,J=6Hz), 1.25(3H.t,J=7.2Hz), 1.86-1.96(2H,m), 2.82(2H,t,J=7.6Hz), 3.14(2H,q,J=7.2Hz), 3.33-3.43(4H,m), 3.38(2H,t,J=6.4Hz), 3.50(1H,qui,J=6Hz), 7.37(1H,d,J=8Hz), 7.61(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.74(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.96(1H,d,J=8Hz), 8.11(1H,s), 8.11(1H,d,J=8Hz), 8.41(1H,dd,J=8Hz,2.4Hz), 9.27(1H,d,2.4Hz).

ESI-Mass; 419(MH^+).

Example 144 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(3-methoxybutyl)pyridin-5-yl]isoquinoline oxalate

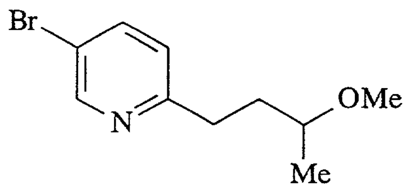
(144-1) 5-Bromo-2-(3-methoxy-1-butynyl)pyridine



5-Bromo-2-(3-hydroxy-1-butynyl)pyridine (5.426 g) was dissolved in tetrahydrofuran (60 ml), followed by the sequential addition of triethylamine (10 ml) and methanesulfonyl chloride (2.2 ml) under ice-cooling, and the resulting mixture was stirred for 1 hr. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was dissolved in methanol (16 ml), and under ice-cooling, 28% sodium methoxide/methanol solution (4.6 ml) was added thereto and the resulting mixture was stirred at room temperature overnight. The reaction mixture was evaporated and partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a brown oil (1.968 g, yield; 34%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.54(3H,d,J=6.4Hz), 3.85(1H,t,J=6.4Hz), 3.86(1H,t,J=6.4Hz), 7.33(1H,dd,J=8.4Hz,0.8Hz), 7.79(1H,dd,J=8.4Hz,2.4Hz), 8.64(1H,dd,J=2.4Hz,0.8Hz).

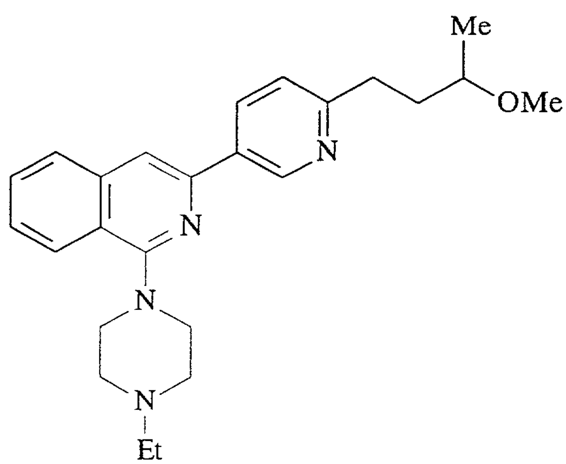
(144-2) 5-Bromo-2-(3-methoxybutyl)pyridine



In the same manner as in Example 139-2, the title compound was obtained as a brown oil (1.125 g, yield; 56%) from 5-bromo-2-(3-methoxy-1-butynyl)pyridine (1.968 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(3H,d,J=6.4Hz), 1.83-1.90(2H,m), 3.32(4H,s), 7.07(1H,d,J=8.4Hz), 7.70(1H,dd,J=8.4Hz,2.4Hz), 8.57(1H,d,J=2.4Hz).

(144-3) 1-(1-Ethylpiperazin-4-yl)-3-[2-(3-methoxybutyl)pyridin-5-yl]isoquinoline oxalate



In the same manner as in Example 167-2, the oxalate of the title compound was obtained as a yellowish brown amorphous (352 mg, yield; 58%) from 5-bromo-2-(3-methoxybutyl)pyridine (1.125 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (377 mg).

Oxalate:

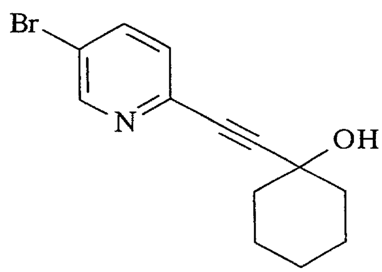
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.11(3H,d,J=6.4Hz),

1.24(3H,t,J=7.2Hz), 1.75-1.90(2H,m), 2.74-2.87(2H,m), 3.13(2H,q,J=7.2Hz), 3.22(3H,s), 3.26-3.34(1H.m), 3.32-3.42(4H,br-s), 7.37(1H,d,J=8Hz), 7.61(1H,dd,J=8Hz,7Hz), 7.74(1H,dd,J=8Hz,7Hz), 7.96(1H,d,J=8Hz), 8.11(1H,s), 8.12(1H,d,J=8Hz), 8.41(1H,dd,J=8Hz,2.4Hz), 9.26(1H,d,J=2.4Hz).

ESI-Mass; 405(MH^+).

Example 145 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-{2-[2-(2-hydroxy-2-cyclohexyl)ethynyl]pyridin-4-yl}isoquinoline oxalate

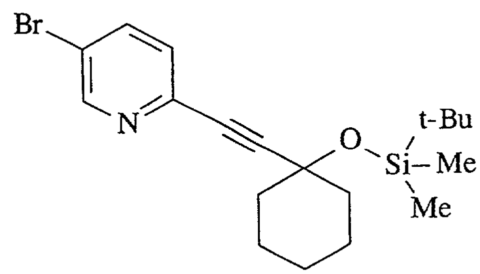
(145-1) 5-Bromo-2-[2-(1-hydroxycyclohexyl)ethynyl]pyridine



In the same manner as in Example 139-1, the title compound was obtained as a pale brown solid (14.305 g, yield; 85%) from 2,5-dibromopyridine (14.213 g) and 1-ethynylcyclopentanol (7.451 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.25-1.36(1H,m), 1.52-1.80(6H,m), 2.00-2.06(2H,m), 2.40-2.45(1H,m), 7.31(1H,d,J=8.4Hz), 7.78(11H,dd,J=8.4Hz,2.4Hz), 8.63(1H,d,J=2.4Hz).

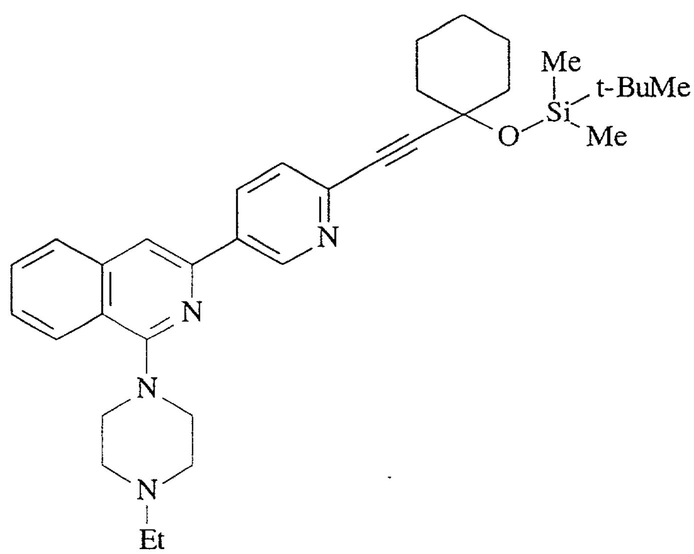
(145-2) 5-Bromo-2-[2-[1-(tert-butyldimethylsilyloxy)cyclohexyl]ethynyl]pyridine



In the same manner as in Example 138-3, the title compound was obtained as a pale yellow oil (4 g, yield; 100%) from 5-bromo-2-[2-(1-hydroxycyclohexyl)ethynyl]pyridine (2.802 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.21(6H,s), 0.90(9H,s), 1.32-1.94(10H,m), 7.28(1H,d,J=8.4Hz), 7.77(1H,dd,J=8.4Hz,2.4Hz), 8.64(1H,d,J=2.4Hz).

(145-3) 1-(1-Ethylpiperazin-4-yl)-3-[2-[2-[2-(t-butyldimethylsilyloxy)-2-cyclohexyl]ethynyl]pyridin-4-yl]isoquinoline or compound identified by the following analytical data and synthetic procedures

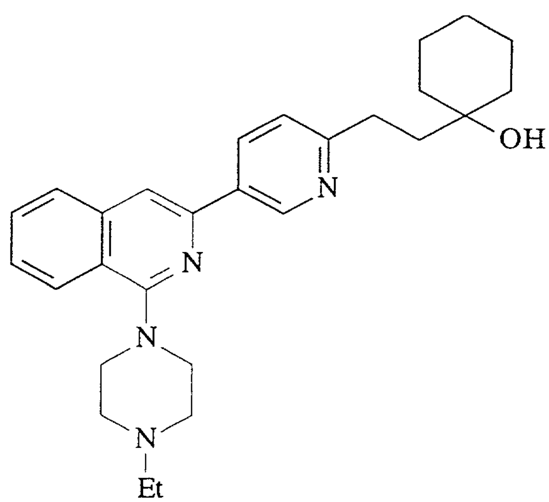


In the same manner as in Example 167-2, the title compound

was obtained as a yellow oil (156 mg, yield; 21%) from 5-bromo-2-{2-[1-(t-butyldimethylsilyloxy)cyclohexyl]ethynyl}pyridine (4 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (446 mg).

^{1}H-NMR(400MHz,$CDCl_3$); δ(ppm) 0.26(6H,s), 0.92(9H,s), 1.14(3H,t,J=7.2Hz), 1.05-1.75(10H,m), 2.55(2H,q,J=7.2Hz), 2.74(4H,t,J=4.4Hz), 3.59(4H,t,J=4.4Hz), 7.49(1H,dd,J=8.4Hz,0.8Hz), 7.50((1H,ddd,J=8Hz,7Hz,1.2Hz), 7.61(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.69(1H,s), 7.80(1H,d,J=8Hz), 8.07(1H,d,J=8Hz), 8.40(1H,dd,J=8.4Hz,2.4Hz), 9.35(1H,dd,J=2.4Hz,0.8Hz).

(145-4) 1-(1-Ethylpiperazin-4-yl)-3-[2-[2-(2-hydroxy-2-cyclohexyl)ethynyl]pyridin-4-yl]isoquinoline oxalate or compound identified by the following analytical data and synthetic procedures



1-(1-Ethylpiperazin-4-yl)-3-[2-{2-[1-(t-butyldimethylsilyloxy)-2-cyclohexyl]ethynyl}pyridin-4-yl]]isoquinoline (156 mg) was dissolved in tetrahydrofuran (10

ml), followed by the addition of 1M tetrabutylammonium fluoride/tetrahydrofuran solution (0.6 ml), and the resulting mixture was stirred at room temperature for 30 min. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was then treated in the same manner as in Example 131, to give the oxalate of the title compound as a yellow amorphous (110 mg, yield; 67%).

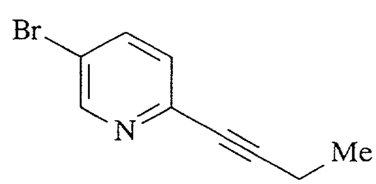
Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.23(3H,t,J=7.2Hz), 1.28-1.64(8H,m), 1.71-1.78(2H,m), 2.79-2.86(2H,m), 3.06(2H,q,J=7.2Hz), 3.26-3.36(4H,br-s), 3.38-3.76(4H,br-s), 7.36(1H,d,J=8Hz), 7.60(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.74(1H,ddd,J=8Hz,7Hz,1.2Hz), 7,69(1H,s), 8.10(1H,dd,J=8Hz,2.4Hz), 9.24(1H,d,J=2.4Hz).

ESI-Mass; 445(MH^+).

Example 146 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(1-butyn-1-yl)pyridin-5-yl]isoquinoline

(146-1) 5-Bromo-2-(1-butynyl)pyridine

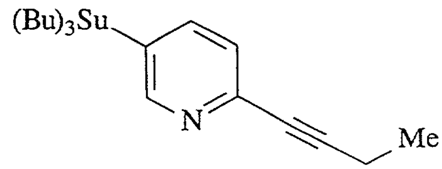


In the same manner as in Example 139-1, the title compound was obtained as a brown solid (13.113 g, yield; 60%) from 2,5-dibromopyridine (24.7 g) and 1-butyne (5.63 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.26(3H,t,J=7.6Hz),

2.44(2H,q,J=7.6Hz), 7.74(1H,dd,J=8.4Hz,2.4Hz), 8.59(1H,d,J=2.4Hz).

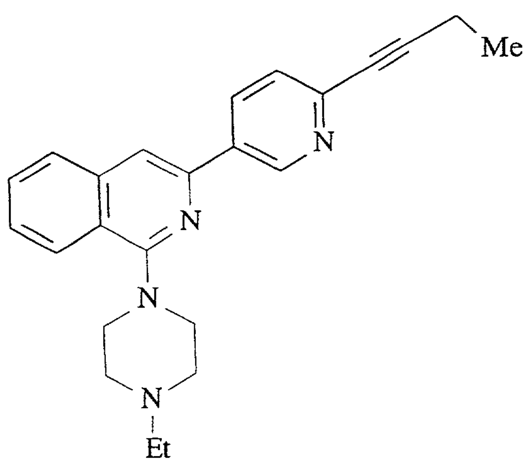
(146-2) 2-(1-Butynyl)-5-tributylstannylpyridine



In the same manner as in Example 161-2, the title compound was obtained as a pale green oil (1.331 g, yield; 25%) from 5-bromo-2-(1-butynyl)pyridine (2.521 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.88(9H,t,J=7.6Hz), 1.06-1.11(6H,m), 1.26(3H,t,J=7.6Hz), 7.30(1H,dd,J=7.4Hz,1.2Hz), 7.67(1H,dd,J=7.4Hz,1.2Hz), 8.52(1H,t,J=1.2Hz).

(146-3) 1-(1-Ethylpiperazin-4-yl)-3-[2-(1-butynyl)pyridin-5-yl]isoquinoline



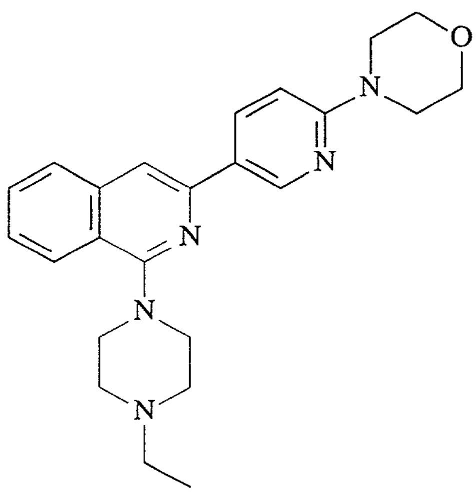
In the same manner as in Example 161-2, the title compound was obtained as a yellow amorphous (155 mg, yield; 27%) from 2-(1-butynyl)-5-tributylstannylpyridine (1.331 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (466 mg).

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(3H,t,J=7.2Hz), 1.29(3H,t,J=7.2Hz), 2.50(2H,q,J=7.2Hz), 2.56(2H,q,J=7.2Hz), 2.75(4H,t,J=4.4Hz), 3.59(4H,t,J=4.4Hz), 7.46(1H,d,J=8Hz), 7.50(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.62(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.71(1H,s), 7.82(1H,d,J=8Hz), 8.09(1H,d,J=8Hz), 8.40(1H,dd,J=8Hz,2.4Hz), 9.29(1H,d,J=2.4Hz).

ESI-Mass; 371(MH^+).

Example 147 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[2-(morpholin-4-yl)pyridin-5-yl]isoquinoline trihydrochloride



3-Bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.27 g) and [2-(morpholin-4-yl)pyridin-5-yl]tributylstannum (3.03 g) were reacted in the presence of tetrakistriphenylphosphine dichloride (0.50 g) in xylene (50 ml) at 140°C for 5 hr. The reaction solution was concentrated. Ethyl acetate and an aqueous solution of saturated sodium bicarbonate were added to the resulting residue, and then it was partitioned. The resulting organic layer was washed with water and brine, and

then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.39 g of the free compound of the title compound as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.75(br-t,4H), 3.54(m,4H), 3.59(br-t,4H), 3.85(m,4H), 6.72(d,J=8.8Hz,1H), 7.42(br-t,1H), 7.55(s,1H), 7.56(br-t,1H), 7.75(d,J=8.0Hz,1H), 8.04(d,J=8.0Hz,1H), 8.27(dd,J=8.4,2.4Hz,1H), 9.02(d,J=2.4Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 0.51 g of the title compound as a white powder.

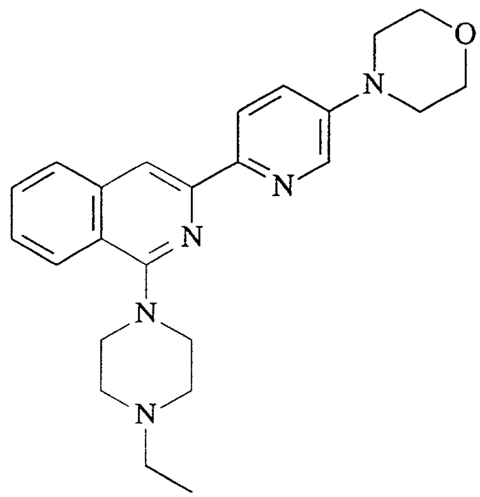
Hydrochloride:

m.p.; 186°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 3.23(m,2H), 3.36(m,2H), 3.51(br-t,2H), 3.63(br-d,2H), 3.68(m,4H), 3.77(m,4H), 4.00(br-d,2H), 7.26(m,1H), 7.61(br-t,1H), 7.75(br-t,1H), 7.95(br-d,1H), 8.08(s,1H), 8.11(br-d,1H), 8.54(m,1H), 8.86(br-s,1H).

MS(FAB) m/z 404$(M+H)^+$.

Example 148 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[5-(morpholin-4-yl)pyridin-2-yl]isoquinoline trihydrochloride



3-(5-Bromopyridin-2-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline (0.21 g) and morpholine (0.12 ml) were reacted in the presence of tetrakistriphenylphosphine dichloride (0.30 g) in xylene (30 ml) at 140°C for 5 hr. The reaction solution was concentrated. Ethyl acetate and an aqueous solution of saturated sodium bicarbonate were added to the resulting residue, and partitioned. The resulting organic layer was washed with water and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 47 mg of the free compound of the title compound as a colorless oil.

Free compound:

^{1}H-NMR(400MHz, $CDCl_3$); δ (ppm) 1.20(t,J=7.2Hz,3H), 2.58(q,J=7.2Hz,2H), 2.79(br-s,4H), 3.27(m,4H), 3.59(br-s,4H), 3.91(m,4H), 7.30(dd,J=8.8,2.8Hz,1H), 7.46(br-t,1H), 7.58(br-t,1H), 7.85(d,J=8.0Hz,1H), 8.07(d,J=8.0Hz,1H), 8.26(s,1H), 8.37(d,J=2.8Hz,1H), 8.41(d,J=8.8Hz,1H).

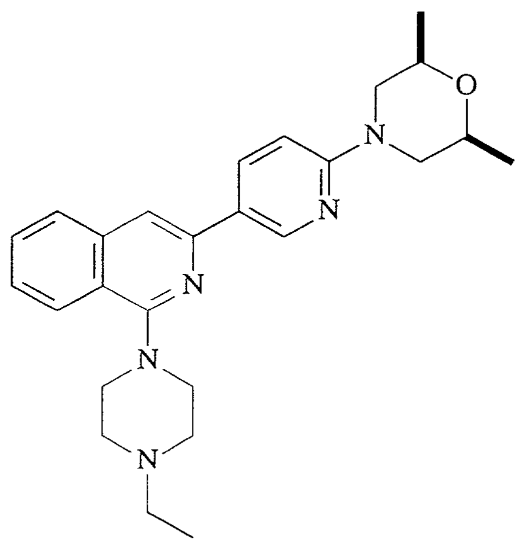
The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 52 mg of the free compound of the title compound as a white powder.

Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 3.24(m,2H), 3.32-3.42(m,6H), 3.50-3.65(m,4H), 3.81(m,4H), 4.13(br-d,2H), 7.69(br-t,1H), 7.81(br-t,1H), 7.94(br,1H), 8.04(br-d,1H), 8.16(br-d,1H), 8.36(br-d,1H), 8.45(br-s,1H), 8.48(br-d,1H).

MS (FAB) m/z 404(M+H)$^+$.

Example 149 Synthesis of 3-[2-(2,6-dimethylmorpholin-4-yl)pyridin-5-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline trihydrochloride



3-Bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (2.00 g) and [2-(2,6-dimethylmorpholin-4-yl)pyridin-5-yl]tributylstannum (5.70 g) were reacted in the presence of tetrakistriphenylphosphine dichloride (0.50 g) in xylene (70

ml) at 140°C for 5 hr. The reaction solution was concentrated. Ethyl acetate and an aqueous solution of saturated sodium bicarbonate were added to the resulting residue, for partitioning. The resulting organic layer was washed with water and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.76 g of the free compound of the title compound as a colorless oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.30(d,J=6.0Hz,6H), 2.57(q,J=7.2Hz,2H), 2.60(dd,J=13.0,10.4Hz,6H), 2.76(br-t,4H), 3.60(br-t,4H), 3.76(ddd,J=10.4,6.0,2.0Hz,2H), 4.14(dd,J=13.0,2.0,2H), 6.72(d,J=8.8Hz,1H), 7.42(br-t,1H), 7.55(s,1H), 7.57(br-t,1H), 7.76(d,J=8.0,1H), 8.04(d,J=8.0,1.0Hz,1H), 8.26(dd,J=8.0,2.4Hz,1H), 9.02(d,J=2.4Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 1.08 g of the hydrochloride of the title compound as a white powder.

Hydrochloride:

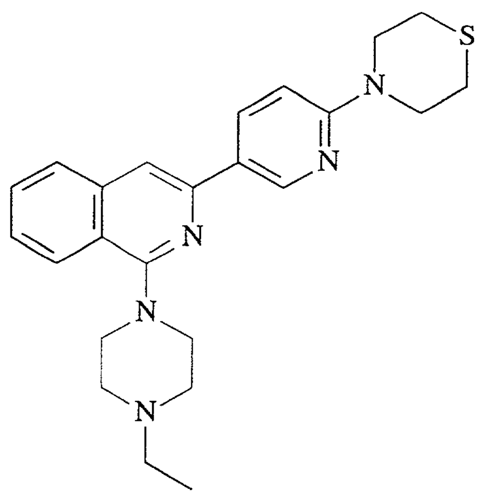
m.p.; 180°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.19(d,J=5.6Hz,6H), 1.32(t,J=7.2Hz,3H), 2.62-2.68(m,2H), 3.24(m,2H), 3.37(m,2H), 3.48(br-t,2H), 3.60-3.70(m,4H), 4.01(br-d,2H), 4.29(br-d,2H),

7.24(m,1H), 7.60(br-t,1H), 7.55(br-t,1H), 7.75(br-t,1H), 7.95(br-d,1H), 8.05(br-s,1H), 8.11(br-d,1H), 8.49(m,1H), 8.86(br-s,1H).

MS(FAB) m/z 432(M+H)$^+$.

Example 150 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[2-(thiomorpholin-4-yl)pyridin-5-yl]isoquinoline trihydrochloride



3-Bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.69 g) and [2-(thiomorpholin-4-yl)pyridin-5-yl]tributylstannum (1.62 g) were reacted in the presence of tetrakistriphenylphosphine dichloride (0.50 g) in xylene (50 ml) at 140°C for 5 hr. The reaction solution was concentrated. Ethyl acetate and an aqueous solution of saturated sodium bicarbonate were added to the resulting residue, for partitioning. The resulting organic layer was washed with water and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene

chloride/methanol system), to give 0.66 g of the free compound of the title compound as a white amorphous.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.24(br-s,3H), 2.64(br-s,2H), 2.70(m,4H), 2.80(br,4H), 3.67(br,4H), 4.04(m,4H), 6.42(d,J=8.8Hz,2H), 7.43(br-t,1H), 7.56(br-t,1H), 7.76(d,J=8.0Hz,1H), 8.03(d,J=8.0Hz,1H), 8.24(dd,J=8.8,2.4Hz,1H), 9.00(d,J=2.4Hz,1H).

The resulting free compound (0.20 g) was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 0.26 g of the hydrochloride of the title compound as a pale yellow powder.

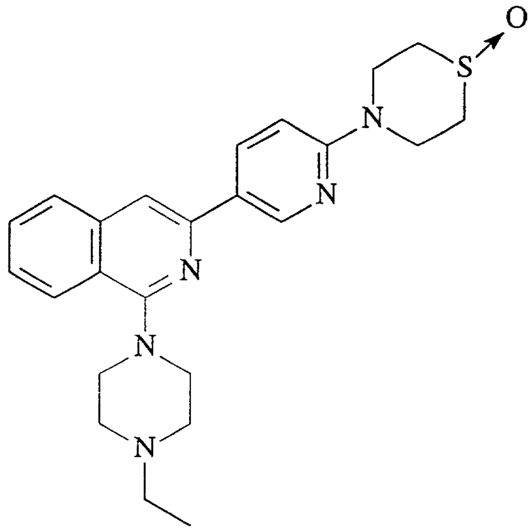
Hydrochloride:

m.p.; 210°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 2.75(br-s,4H), 3.20-3.27(m,2H), 3.47-3.56(m,2H), 3.60-3.66(br-d,2H), 3.97-4.02(br-d,2H), 4.10(br-s,4H), 7.37(m,1H), 7.62(br-t,1H), 7.77(br-t,1H), 7.96(br-d,1H), 8.09-8.14(m,1H), 8.58(m,1H), 8.80(m,1H), 10.9(m,1H).

MS(FAB) m/z 420$(M+H)^+$.

Example 151 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[2-(S-oxythiomorpholin-4-yl)pyridin-5-yl]isoquinoline trihydrochloride



1-(4-Ethylpiperazin-1-yl)-3-[2-(thiomorpholin-4-yl)pyridin-5-yl]isoquinoline (0.10 g) obtained in Example 150 was dissolved in dichloromethane (10 ml), and the resulting solution was reacted with 3-chloroperbenzoic acid (56 mg) under ice-cooling for 1 hr. The reaction solution was partitioned between ethyl acetate and an aqueous solution of saturated sodium bicarbonate. The resulting organic layer was washed with water and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 28 mg of the free compound of the title compound as a colorless oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.22(t,J=7.2Hz,3H), 2.63(q,J=7.2Hz,2H), 2.79-2.88(m,8H), 3.65(br-s,4H), 4.22(m,4H), 6.82(d,J=8.8Hz,2H), 7.45(br-t,1H), 7.58(br-t,1H), 7.76(d,J=8.0Hz,1H), 8.03(d,J=8.0Hz,1H),

8.28(dd,J=8.8,2.4Hz,1H), 9.01(d,J=2.4Hz,1H).

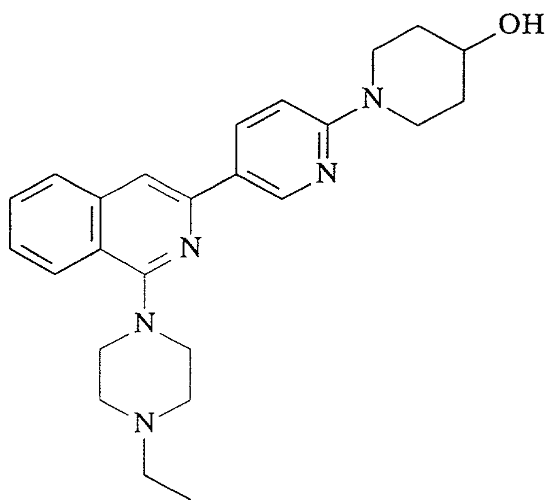
The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 40 mg of the hydrochloride of the title compound as a yellow powder.

Hydrochloride:

m.p.; 170°C

MS(FAB) m/z 436$(M+H)^+$.

Example 152 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[2-(4-hydroxypiperidin-1-yl)pyridin-5-yl]isoquinoline trihydrochloride



3-Bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.16 g) and {2-[4-(t-butyldimethyloxy)piperidin-1-yl]pyridin-5-yl}tributylstannum (1.37 g) was reacted in the presence of tetrakistriphenylphosphine dichloride (0.30 g) in xylene (30 ml) at 140°C for 5 hr. The reaction solution was concentrated. A 2N aqueous solution of hydrochloric acid was added to the resulting residue, and then reacted at 50°C for 1 hr. The

reaction solution was basified with a 2N aqueous solution of sodium hydroxide, and then it was extracted with ethyl acetate. The resulting organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.26 g of the free compound of the title compound as a colorless amorphous.

Free compound:

^{1}H-NMR(400MHz, $CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.33(dd,J=12.0,4.0Hz,2H), 1.43(dt,J=0.8,6.0Hz,1H), 1.86(br-d,J=12Hz,2H), 2.56(q,J=7.2Hz,2H), 2.76(br-s,4H), 2.92(dt,2.4,12.8Hz,2H), 3.55(t,J=6Hz,2H), 3.59(br-s,4H), 4.44(br-d,J=12.8,2H), 6.76(d,J=8.8Hz,1H), 7.42(br-t,1H), 7.54(s,1H), 7.75(d,J=8.0Hz,1H), 8.04(d,J=8.0Hz,1H), 8.23(dd,J=8.8,2.4Hz,1H), 9.01(d,J=2.4Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 0.30 g of the hydrochloride of the title compound as a yellow powder.

Hydrochloride:

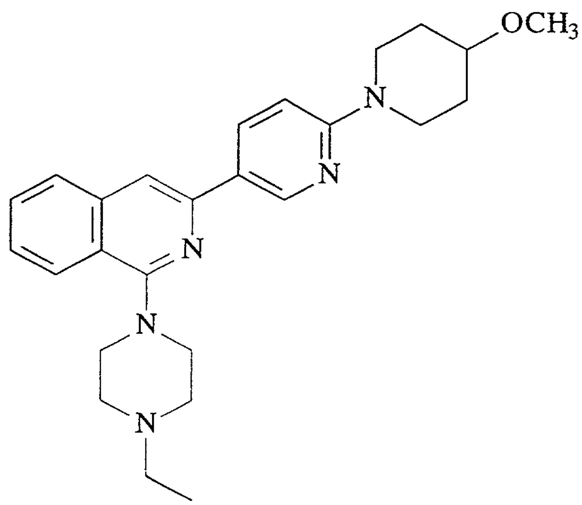
m.p.; 188°C

^{1}H-NMR(400MHz, DMSO-d_6); δ (ppm) 1.27(br-d,J=13.4Hz,3H), 1.34(t,J=7.2Hz,3H), 1.73-1.86(m,1H), 1.83(br-d,J=13.4,2H), 3.23(m,2H), 3.31(m,2H), 3.32-3.37(m,2H), 3.42-3.56(m,4H), 3.98(br-d,2H), 4.41(br-d,2H), 7.52(br-d,1H), 7.64(br-

t,J=7.6Hz,1H), 7.78(br-t,J=7.6Hz,1H), 7.97(br-d,J=7.6Hz,1H), 8.11-8.15(m,1H), 8.13(s,1H), 8.65(br-d,J=7.6Hz,1H), 8.68(br-s,1H), 11.14(br-s,1H).

MS(FAB) m/z 432$(M+H)^+$.

Example 153 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[2-(4-methoxypiperidin-1-yl)pyridin-5-yl]isoquinoline trihydrochloride



3-Bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.83 g) and [2-(4-methoxypiperidin-1-yl)pyridin-5-yl]tributylstannum (0.94 g) were reacted in the presence of tetrakistriphenylphosphine dichloride (0.40 g) in xylene (30 ml) at 140°C for 5 hr. The reaction solution was concentrated and partitioned between ethyl acetate and water. The resulting organic layer was washed with water and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.61 g of the free compound of the title compound as a pale yellow

oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.65(m,2H), 2.56(q,J=7.2Hz,2H), 2.76(br-s,4H), 3.31(ddd,J=13.2,9.6,3.6Hz,2H), 3.40(s,3H), 3.59(br-s,4H), 4.06(m,2H), 6.77(d,J=8.8Hz,1H), 7.42(br-t,1H), 7.54(s,1H), 7.76(d,J=8.0Hz,1H), 8.04(d,J=8.0Hz,1H), 8.23(dd,J=8.8,2.4Hz,1H), 9.01(d,J=2.4Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 0.62 g of the hydrochloride of the title compound as a white powder.

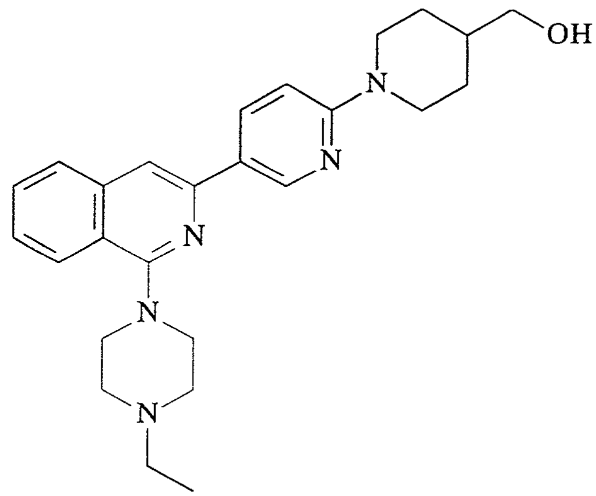
Hydrochloride:

m.p.; 170°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.35(t,J=7.2Hz,3H), 1.58-1.68(m,2H), 1.95-2.04(m,2H), 3.23(m,2H), 3.31(s,3H), 3.38(m,2H), 3.51-3.59(m,5H), 3.64(m,2H), 3.97(br-d,2H), 4.02(m,2H), 7.54(br-d,1H), 7.64(br-t,1H), 7.78(br-t,1H), 7.97(br-d,1H), 8.11-8.15(m,2H), 8.65-8.70(m,2H), 11.34(br-s,1H).

MS(FAB) m/z 432$(M+H)^+$.

Example 154 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[2-(4-hydroxymethylpiperidin-1-yl)pyridin-5-yl]isoquinoline trihydrochloride



3-Bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.35 g) and [2-(4-ethoxycarbonylpiperidin-1-yl)pyridin-5-yl]tributylstannum (1.71 g) were reacted in the presence of tetrakistriphenylphosphine dichloride (0.40 g) in xylene (50 ml) at 140°C for 5 hr. The reaction solution was concentrated and partitioned between ethyl acetate and water. The resulting organic layer was washed with water and brine, and then dried over magnesium sulfate. The solvent was evaporated. The resulting residue in a pale yellow oil was dissolved in tetrahydrofuran (30 ml) and reacted with lithium aluminium hydride (1.9 ml, 1M-THF solution). Water (0.07 ml), a 5N aqueous solution of sodium hydroxide (0.07 ml) and water (0.21 ml) were added to the reaction solution in this order, which was stirred at room temperature for 1 hr. The reaction solution was filtered, and the resulting insoluble matters were washed with ethyl acetate, while the resulting filtrate was concentrated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system),

to give 0.78 g of the free compound of the title compound as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.33(dd,J=12.0,4.0Hz,2H), 1.43(dt,J=0.8,6.0Hz,1H), 1.86(br-d,J=12,2H), 2.56(q,J=7.2Hz,2H), 2.76(br-s,4H), 2.92(dt,2.4,12.8Hz,2H), 3.55(t,J=6Hz,2H), 3.59(br-s,4H), 4.44(br-d,J=12.8,2H), 6.76(d,J=8.8Hz,1H), 7.42(br-t,1H), 7.54(s,1H), 7.75(d,J=8.0Hz,1H), 8.04(d,J=8.0Hz,1H), 8.23(dd,J=8.8,2.4Hz,1H), 9.01(d,J=2.4Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 0.45 g of the hydrochloride of the title compound as a white powder.

Hydrochloride:

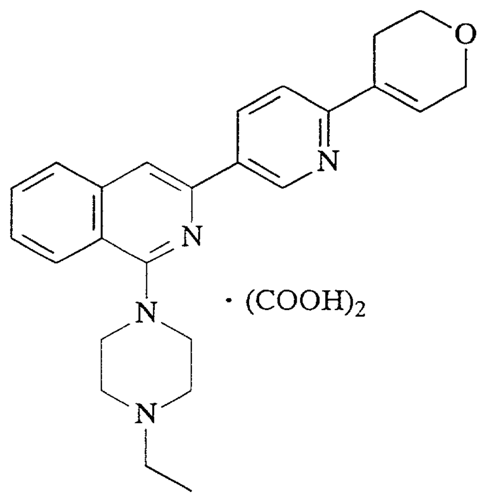
m.p.; 188°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.27(br-d,J=13.4Hz,3H), 1.34(t,J=7.2Hz,3H), 1.73-1.86(m,1H), 1.83(br-d,J=13.4,2H), 3.23(m,2H), 3.31(m,2H), 3.32-3.37(m,2H), 3.42-3.56(m,4H), 3.98(br-d,2H), 4.41(br-d,2H), 7.52(br-d,1H), 7.64(br-t,J=7.6Hz,1H), 7.78(br-t,J=7.6Hz,1H), 7.97(br-d,J=7.6Hz,1H), 8.11-8.15(m,1H), 8.13(s,1H), 8.65(br-d,J=7.6Hz,1H), 8.68(br-s,1H), 11.14(br-s,1H).

MS(FAB) m/z 432$(M+H)^+$.

Example 155 Synthesis of 3-[2-(5,6-dihydro-2H-pyran-4-yl)pyridin-5-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline

<u>oxalate</u>



In the same manners sequentially as in Examples 161-2 and 20, a yellow oil was obtained (127 mg, yield; 90%) from 5-bromo-2-(5,6-dihydro-2H-pyran-4-yl)pyridine (432 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (111 mg). The resulting compound was converted into a oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 156-159°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.23(br,3H), 2.51(br,2H), 3.06(br,2H), 3.32(br,4H), 3.67(br,4H), 3.84(br,2H), 4.26(br,2H), 6.47(s,1H), 7.63(br,1H), 7.96(d,J=8.0Hz,1H), 8.06-8.13(m,2H), 8.38(d,J=8.0Hz,1H), 8.45(s,1H), 8.78(s,1H).

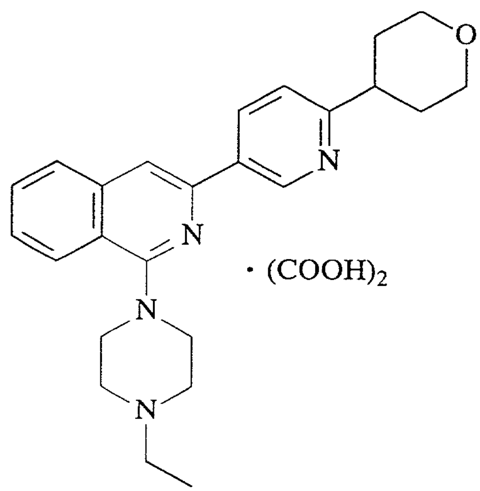
MS(FAB) m/z 401(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 2.54(q,J=7.2Hz,2H), 2.88(t,J=8.0Hz,1H), 2.73(br,4H),

3.52(br,4H), 3.99(t,J=5.6Hz,2H), 4.38(q,J=2.8Hz,2H), 6.28(br,1H), 7.49(t,J=8.0Hz,1H), 7.61(t,J=8.0Hz,1H), 7.80(dd,J=8.4,2.4Hz,1H), 7.89(d,J=8.0Hz,1H), 8.10(d,J=8.0Hz,1H), 8.38(s,1H), 8.49(d,J=8.4Hz,1H), 8.74(d,J=2.4Hz,1H).

Example 156 Synthesis of 3-[2-(tetrahydropyran-4-yl)pyridin-5-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



In the same manners sequentially as in Examples 161-2 and 20, an oil was obtained from 5-bromo-2-(tetrahydropyran-4-yl)pyridine (745 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (300 mg). Methanol (10 ml) and palladium-carbon catalyst (25 mg) were added to the oil (387 mg), and then reacted in hydrogen atmosphere overnight. The resulting reaction solution was filtered through Celite, and then evaporated. The resulting residue was basified by adding a 1N aqueous solution of sodium hydroxide thereto, and then it was partitioned between ethyl acetate and water. The resulting

organic layer was washe with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system), to give a yellow oil (260 mg, yield; 69%). The resulting oil was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 158-160°C

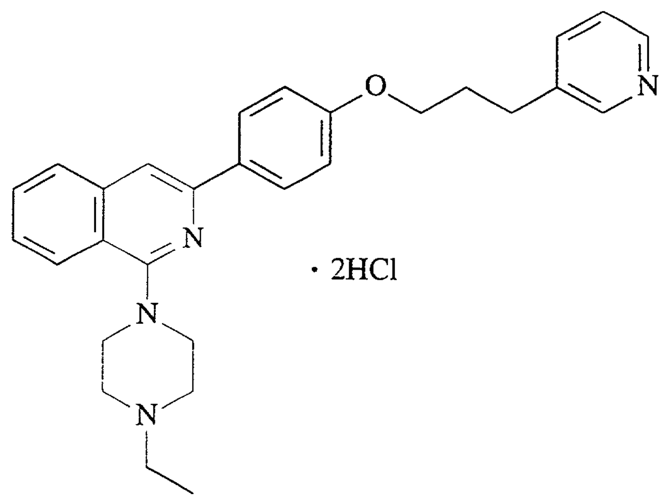
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.27(t,J=7.2Hz,3H), 1.76(br,4H), 2.92(br,1H), 3.19(br,2H), 3.30-3.85(m,10H), 3.99(d,J=11.2Hz,2H), 7.65(t,J=8.0Hz,1H), 7.76(t,J=8.0Hz,1H), 7.86(dd,J=8.4,2.0Hz,1H), 8.09(d,J=8.0Hz,1H), 8.14(d,J=8.4Hz,1H), 8.37(d,J=8.0Hz,1H), 8.46(s,1H), 8.61(d,J=2.0Hz,1H).

MS(FAB) m/z 403(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.19(t,J=6.8Hz,3H), 1.82-1.92(m,4H), 2.57(q,J=6.8Hz,2H), 2.78(br,4H), 2.78-2.98(m,1H), 3.55-3.59(m,6H), 4.11-4.14(m,2H), 7.50(t,J=8.4Hz,1H), 7.61(t,J=8.4Hz,1H), 7.68(dd,J=8.4,2.4Hz,1H), 7.89(d,J=8.4Hz,1H), 8.11(d,J=8.4Hz,1H), 8.36(s,1H), 8.48(d,J=8.4Hz,1H), 8.57(d,J=2.4Hz,1H).

Example 157 Synthesis of 3-[4-[3-(3-pyridyl)propoxy]phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



· 2HCl

In the same manner as in Example 51, the free compound of the title compound was obtained (62 mg, yield; 23%) from 3-(4-hydroxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline (201 mg) and 3-(3-methanesulfonate propyl)pyridine (194 mg). The resulting free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

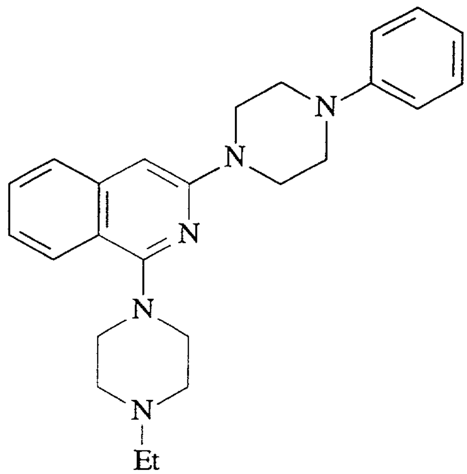
Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.19(t,J=7.2Hz,3H), 2.10-2.18(m,2H), 2.57(q,J=7.2Hz,2H), 2.78(br,4H), 2.85(t,J=7.6Hz,2H), 3.60(br,4H), 4.04(t,J=6.0Hz,2H), 6.98(d,J=8.8Hz,2H), 7.22(dd,J=7.6,4.4Hz,1H), 7.43(dt,J=8.0,1.2Hz,1H), 7.53-7.56(m,1H), 7.56(dt,J=8.0,1.2Hz,1H), 7.62(s,1H), 7.76(d,J=8.0Hz,1H), 8.05(d,J=8.0Hz,1H), 8.11(d,J=8.8Hz,2H), 8.46(dd,J=4.4,1.6Hz,1H), 8.51(d,J=2.0Hz,1H).

MS(FAB) m/z 453(M+H)$^+$.

Example 158 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(1-

phenylpiperazin-4-yl)isoquinoline



1-(1-Ethylpiperazin-4-yl)-3-bromoisoquinoline (631 mg) was dissolved in dioxane (15 ml), followed by the addition of 1-phenylpiperazine (331 mg), tris(dibenzylideneacetone)(chloroform)dipalladium (0) (10 mg), tri-o-tolylphosphine (12 mg) and t-butoxysodium (231 mg), and the resulting mixture was stirred in nitrogen atmosphere at 100°C overnight. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$), evaporated, and then purified by (NH) silica gel column chromatography (ethyl acetate/hexane system). The resulting product was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as a gray amorphous (196 mg, yield; 20%).

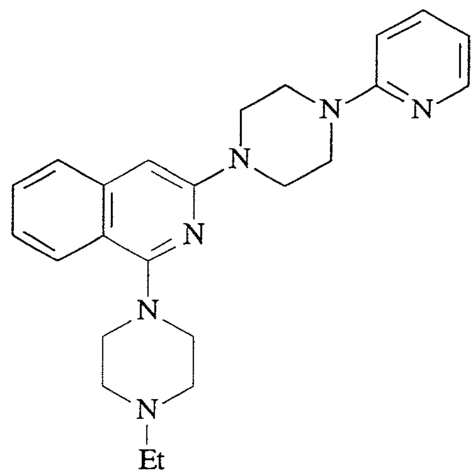
Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.22(3H,t,J=7.2Hz), 3.08(2H,q,J=7.2Hz), 3.24-3.32(8H,m), 3.46-3.62(4H,m), 3.63(4H,t,J=4.4Hz), 6.67(1H.s), 6.80(2H,d,J=8.8Hz),

7.21(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.23(1H,dd,J=8.8Hz,7.2Hz),
7.49(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.63(1H,d,J=8Hz),
7.87(1H,d,J=8Hz).

ESI-Mass; 402(MH^+).

Example 159 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[1-(2-pyridyl)piperazin-4-yl]isoquinoline



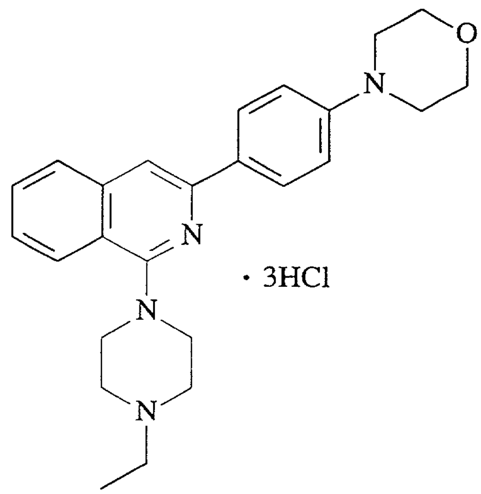
In the same manner as in Example 158, the oxalate of the title compound was obtained as a pale amorphous (533 mg, yield; 42%) from 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (760 mg) and 1-(2-pyridyl)piperazine (1.162 mg).

Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.23(3H,t,J=7.2Hz), 3.10(2H,q,J=7.2Hz), 3.26-3.36(4H,m), 3.46-3.64(4H,m), 3.57-3.66(8H,m), 6.65(1H,ddd,J=7Hz,5Hz,0.8Hz), 6.66(1H,s), 6.89(1H,d,J=8.8Hz), 7.21(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.48(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.55(1H,ddd,J=8.8Hz,7Hz,2Hz), 7.62(1H,d,J=8Hz), 7.87(1H,d,J=8Hz), 8.13(1H,ddd,J=5Hz,2Hz,0.8Hz).

ESI-Mass ; 403(MH^+).

Example 160 Synthesis of 3-[4-(4-morpholinyl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline dihydrochloride



4-(4-Morpholinyl)benzonitrile obtained by reacting 4-fluorobenzonitrile (10.89 g) and morpholine (7.84 g) in the presence of potassium carbonate (12.42 g) in dimethyl sulfoxide (45 ml) was reacted with N-methyl-o-toluamide (8.019 g) according to Example 10-1, to give 6.840 g of 3-[4-(4-morpholinyl)phenyl]isoquinolin-1-one.

The resulting 3-[4-(4-morpholinyl)phenyl]isoquinolin-1-one (1.523 g) was reacted in the same manner as in Example 66, and then purified by silica gel column chromatography (chloroform/methanol system), to give 1.623 g of the free compound of the title compound as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.75(br-t,4H), 3.23(t,J=4.8Hz,4H), 3.58(br-t,4H), 3.88(t,J=4.8Hz,4H), 6.99(d,J=9.0Hz,2H),

7.41(br-t,1H), 7.55(br-t,1H), 7.60(s,1H), 7.75(d,J=8.0Hz,1H), 8.05(d,J=8.4Hz,1H), 8.11(d,J=9.0Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give the hydrochloride of the title compound as a yellow powder.

Hydrochloride:

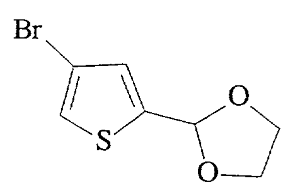
m.p.; 242-245°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 3.19-3.28(m,6H), 3.30-3.38(m,2H), 3.54(br-t,2H), 3.62(br-d,2H), 3.82(br-t,4H), 3.98(br-d,2H), 7.19(d,J=8.6Hz,2H), 7.56(br-t,1H), 7.71(br-t,1H), 7.95(d,J=7.6Hz,1H), 7.98(s,1H), 8.09(d,J=8.4Hz,1H), 8.12(d,J=8.6Hz,2H), 11.13(br-s,1H).

MS(FAB) m/z 403(M+H)$^+$.

Example 161 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(2-hydroxymethylthiophen-4-yl)isoquinoline dihydrochloride

(161-1) 2-(4-Bromothiophen-2-yl)-1,3-dioxolane

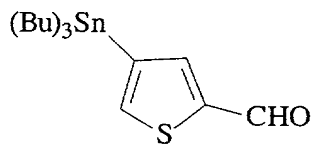


4-Bromo-2-thiophenecarboxyaldehyde (50 g) was dissolved in toluene (500 ml), followed by the addition of ethylene glycol (81 g) and p-toluenesulfonic acid (572 mg). The resulting mixture was heated under reflux overnight with a Dean-Stark apparatus. After cooling as it was, the reaction mixture was washed sequentially with an aqueous solution of saturated

sodium bicarbonate and brine, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a yellow oil (55 g, yield; 89%).

^{1}H-NMR(400MHz, $CDCl_3$); δ (ppm) 4.00-4.13(4H,m), 6.06(1H,s), 7.08(1H,d,J=1.2Hz), 7.21(1H,d,J=1.2Hz).

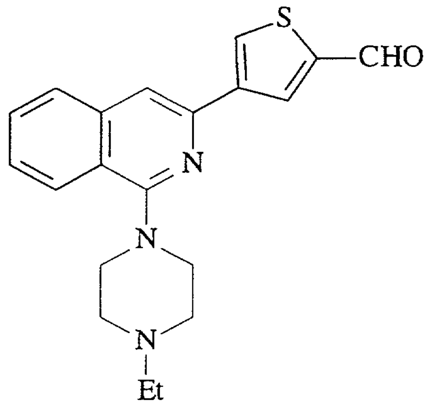
(161-2) 4-Tributylstannyl-2-thiophenecarboxyaldehyde



2-(4-Bromothiophen-2-yl)-1,3-dioxolane (2.351 g) was dissolved in xylene (30 ml), followed by the addition of bis(tributyltin) (5.1 ml) and tetrakis(triphenylphosphine) palladium (116 mg). The resulting mixture was heated under stirring in nitrogen atmosphere at 120°C for 1 hr. After the resulting insoluble matters were filtered off, the resulting solution was evaporated, and then purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a pale yellow oil (1.165 g, yield; 29%).

^{1}H-NMR(400MHz, $CDCl_3$); δ (ppm) 0.90(9H,t,J=7.2Hz), 1.07-1.12(6H,m), 1.28-1.38(6H,m), 1.50-1.58(6H,m), 7.72(1H,d,J=1.2Hz), 7.79(1H,d,J=1.2Hz), 7.79(1H,d,J=1.2Hz), 9.99(1H,d,J=1.2Hz).

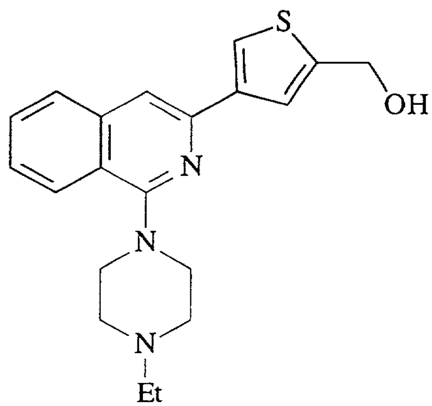
(161-3) 1-(1-Ethylpiperazin-4-yl)-3-(2-formylthiophen-4-yl)isoquinoline



1-(1-Ethylpiperazin-4-yl)-3-bromoisoquinoline (356 mg) was dissolved in xylene (30 ml), followed by the addition of 4-tributylstannyl-2-thiophenecarboxyaldehyde (1.165 g) and tetrakis(triphenylphosphine)palladium (35 mg). The resulting mixture was heated under stirring in nitrogen atmosphere at 120°C overnight. Then, it was diluted with ethyl acetate and extracted with 2N hydrochloric acid. The resulting aqueous layer was washed with ethyl acetate, basified with 8N sodium hydroxide, and then extracted with ethyl acetate. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting product was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a yellow oil (265 mg, yield; 73%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(3H,t,J=7.2Hz), 2.56(2H,q,J=7.2Hz), 2.76(4H,t,J=4.4Hz), 3.57(4H,t,J=4.4Hz), 7.48(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.55((H,ddd,J=8Hz,7Hz,1.2Hz), 7.77(1H,d,J=8Hz), 8.07(1H,d,J=8Hz), 8.37(2H,s), 10.00(1H,s).

(161-4) 1-(1-Ethylpiperazin-4-yl)-3-(2-hydroxymethylthiophen-4-yl)isoquinoline dihydrochloride



1-(1-Ethylpiperazin-4-yl)-3-(2-formylthiophen-4-yl)isoquinoline (141 mg) was dissolved in ethanol (10 ml), followed by the addition of sodium borohydride (8 mg) under ice-cooling, and the resulting mixture was stirred at room temperature for 30 min. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/isopropyl ether, to give the hydrochloride of the title compound as yellow crystals (130 mg, yield; 75%).

Hydrochloride:

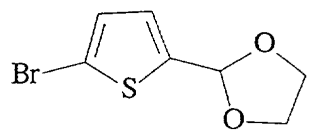
m.p.; 170°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.30(3H,t,J=7.2Hz), 3.15-3.22(2H,m), 3.29(1H,t,J=11Hz), 3.32(1H,t,J=11Hz), 3.49(2H,t,J=13.4Hz), 3.57(2H,d,J=11Hz), 3.94(2H,d,J=13.4Hz), 4.66(2H,s), 7.55(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.62(1H,d,J=1.6Hz), 7.69(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.86(1H,s), 7.89(1H,d,J=8Hz), 8.02(1H,d,J=1.6Hz), 8.05(1H,d,J=8Hz).

ESI-Mass ; 354(MH^+).

Example 162 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(2-hydroxymethylthiophen-5-yl)isoquinoline dihydrochloride

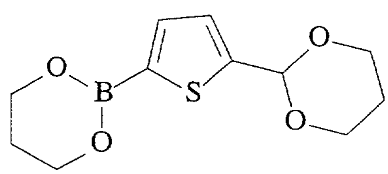
(162-1) 2-(5-Bromothiophen-2-yl)-1,3-dioxolane



In the same manner as in Example 161-1, the title compound was obtained as a brown oil (57.2 g, yield; 93%) from 5-bromo-2-thiophenecarboxaldehyde (50 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 3.96-4.13(4H,m), 6.01(1H,s), 6.90(1H,d,J=3.6Hz), 6.93(1H,d,J=3.6Hz).

(162-2) [5-(1,3-Dioxan-2-yl)thiophen-2-yl]-1,3,2-dioxaborylate

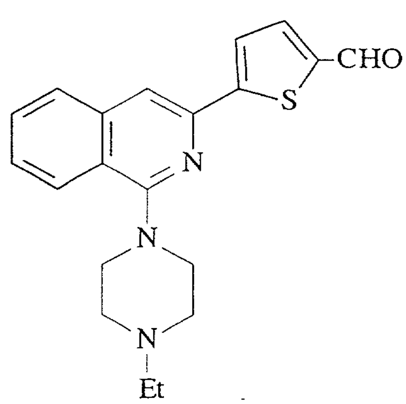


2-(5-Bromothiophen-2-yl)-1,3-dioxolane (2.351 g) was dissolved in tetrahydrofuran (10 ml), to which was then added 2.5 M n-butyl lithium/hexane solution (4 ml) in nitrogen atmosphere at -78 °C, and the mixture was stirred for 30 min. Then, trimethoxyborane (1.3 ml) was added thereto, and the mixture was stirred for 30 min, and then it was stirred at room temperature for 30 min. 2N Hydrochloric acid (10 ml) was added to the reaction mixture, and then the mixture was stirred for 30 min. Thereafter, the resulting mixture was extracted with

ether. The resulting organic layer was evaporated. The resulting residue was dissolved in ether, followed by the addition of trimethylene glycol (529 mg). The resulting mixture was stirred at room temperature for 90 min, and then evaporated. The resulting residue was dissolved in toluene, followed by the addition of trimethylene glycol (3.517 g) and p-toluenesulfonic acid (9 mg), and the resulting mixture was heated under reflux with a Dean-Stark apparatus for 3 hr. After cooling as it was, the reaction mixture was washed with water, dried (over $MgSO_4$) and evaporated, to give the title compound as a pale yellow oil (1.516 g, yield; 60%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.40-1.46(1H,m), 2.00-2.08(2H,m), 2.15-2.28(1H,m), 3.93-4.00(2H,m), 4.13(4H,t,J=5Hz), 4.20-4.28(2H,m), 5.74(1H,s), 7.15(1H,d,J=3.6Hz), 7.40(1H,d,J=3.6Hz).

(162-3) 1-(1-Ethylpiperazin-4-yl)-3-(2-formylthiophen-4-yl)isoquinoline

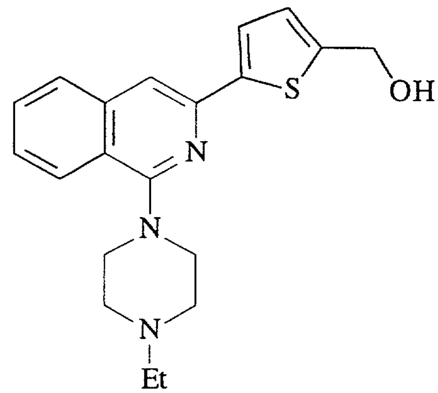


1-(1-Ethylpiperazin-4-yl)-3-bromoisoquinoline (480 mg) was dissolved in N,N-dimethylformamide (12 ml), followed by the

addition of [5-(1,3-dioxan-2-yl)thiophen-2-yl]-1,3,2-dioxaborate (643 mg), tetrakis(triphenylphosphine)palladium (23 mg) and cesium carbonate (977 mg), and the resulting mixture was heated under stirring in nitrogen atmosphere at 100°C overnight. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting product was purified by silica gel column chromatography (toluene/acetone system), and then dissolved in tetrahydrofuran (10 ml). 1N Hydrochloric acid (10 ml) was added thereto, and the mixture was stirred for 1 hr. The reaction solution was basified by adding 5N sodium hydroxide thereto, followed by the extraction with ethyl acetate. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated, to give the title compound as a brown solid (494 mg, yield; 93%).

^{1}H-NMR(400MHz, $CDCl_3$); δ (ppm) 1.17(3H,t,J=7.2Hz), 2.54(2H,q,J=7.2Hz), 2.73(4H,t,J=4.8Hz), 3.62(4H,t,J=4.8Hz), 7.50(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.62(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.66(1H,s), 7.70(1H,d,J=4Hz), 7.77(1H,d,J=4Hz), 7.79(1H,d,J=8Hz), 8.06(1H,d,J=8Hz), 9.92(1H,s).

<u>(162-4) 1-(1-Ethylpiperazin-4-yl)-3-(2-hydroxymethylthiophen-5-yl)isoquinoline dihydrochloride</u>



In the same manner as in Example 161-4, the hydrochloride of the title compound was obtained as a yellow crystals (130 mg, yield; 75%) from 1-(1-ethylpiperazin-4-yl)-3-(2-formylthiophen-5-yl)isoquinoline (120 mg).

Hydrochloride:

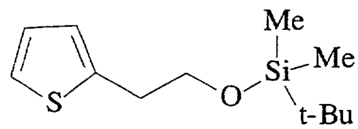
m.p.; 180 °C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.29(3H,t,J=7.2Hz), 3.15-3.25(2H,m), 3.29(1H,t,J=11.2Hz), 3.32(1H,t,J=11.2Hz), 3.45(2H,t,J=13.4Hz), 3.59(2H,d,J=11.2Hz), 3.93(2H,d,J=13.4Hz), 4.63(2H,s), 6.97(1H,d,J=3.6Hz), 7.54(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.61(1H,d,J=3.6Hz), 7.69(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.88(1H,s), 7.89(1H,d,J=8Hz), 8.05(1H,d,J=8Hz).

ESI-Mass; 354(MH^+).

Example 163 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(2-hydroxyethyl)thiophen-5-yl]isoquinoline dihydrochloride

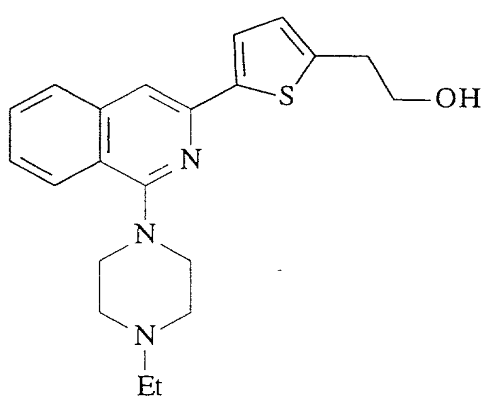
(163-1) 2-[2-(t-Butyldimethylsilyloxy)ethyl]thiophene



2-(2-Thienyl)ethanol (2.6 g) was dissolved in N,N-dimethylformamide (20 ml), followed by the addition of t-butyldimethylsilyl chloride (3.667 g) and imidazole (1.634 g), and the mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a colorless oil (4.87 g, yield; 100%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.03(6H,s), 0.89(9H,s), 3.04(2H,t,J=6.8Hz), 3.82(2H,t,J=6.8Hz), 6.83(1H,dd,J=3.6Hz,1Hz), 6.93(1H,dd,J=5Hz,3.6Hz), 7.13(1H,dd,J=5Hz,1Hz).

<u>(163-2) 1-(1-Ethylpiperazin-4-yl)-3-[2-(2-hydroxyethyl)thiophen-5-yl]isoquinoline dihydrochloride</u>



In the same manner as in Example 167-2, the hydrochloride of the title compound was obtained as yellow brown crystals (722 mg, yield; 64%) from 2-[2-(t-butyldimetylsilyloxy)ethyl]thiophene (2.435 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (809 mg).

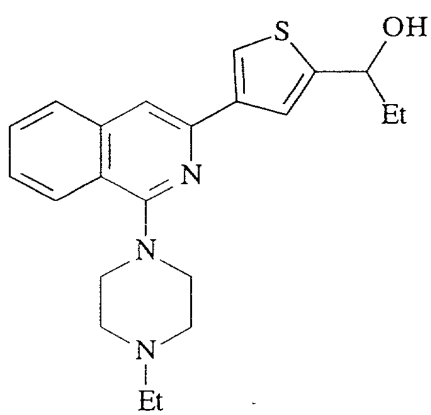
Hydrochloride:

m.p.; 129-134°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.30(3H,t,J=7.2Hz), 2.93(2H,t,J=6.4Hz), 3.15-3.24(2H,m), 3.28(1H,t,J=11.6Hz), 3.31(1H,t,J=11.6Hz), 3.45(2H,t,J=13.2Hz), 3.59(2H,d,J=11.6Hz), 3.63(2H,t,J=6.4Hz), 3.91(2H,d,J=13.2Hz), 6.90(1H,d,J=3.6Hz), 7.52(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.58(1H,d,J=3.6Hz), 7.68(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.85(1H,s), 7.88(1H,d,J=8Hz), 8.04(1H,d,J=8Hz), 10.75(1H,br-s).

ESI-Mass; 368(MH^+).

Example 164 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(1-hydroxypropyl)thiophen-4-yl]isoquinoline hydrochloride



In the same manner as in Example 260, the hydrochloride of the title compound was obtained as a brown amorphous (226

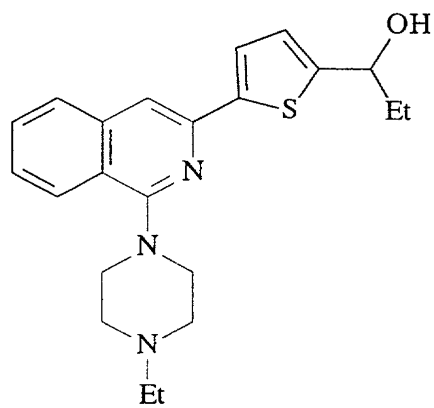
mg, yield; 73%) from 1-(1-ethylpiperazin-4-yl)-3-(2-formylthiophen-4-yl)isoquinoline (233 mg) and 3M ethylmagnesium bromide (0.7 ml).

Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.89(3H,t,J=7.4Hz), 1.22(3H,t,J=7.2Hz), 1.70-1.78(2H,m), 2.97-3.07(2H,br-s), 3.18-3.32(4H,br-s), 3.47-3.72(4H,br-s), 4.72(1H,t,J=6.4Hz), 7.54(1H,dd,J=8Hz,7Hz), 7.58(1H,s), 7.69(1H,dd,J=8Hz,7Hz), 7.84(1H,s), 7.88(1H,d,J=8Hz), 7.98(1H,s), 8.05(1H,d,J=8Hz).

ESI-Mass; 382(MH^{+}).

Example 165 Synthesis of 1-(1-Ethylpiperazin-4-yl)-3-[2-(1-hydroxypropyl)thiophen-5-yl)isoquinoline hydrochloride



In the same manner as in Example 260, the hydrochloride of the title compound was obtained as a brown amorphous (197 mg, yield; 79%) from 1-(1-ethylpiperazin-4-yl)-3-(2-fomylthiophen-5-yl)isoquinoline (181 mg) and 3M ethylmagnesium bromide (0.7 ml).

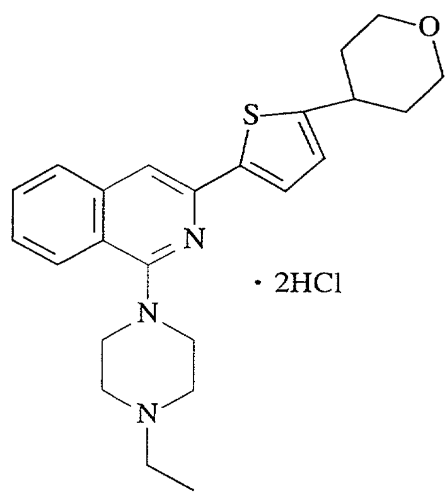
Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.88(3H,t,J=7.4Hz),

1.19(3H,t,J=7.2Hz), 1.68-1.74(2H,m), 2.90-3.02(2H,br-s), 3.10-3.27(4H,br-s), 3.45-3.62(4H,br-s), 4.68(1H,t,J=6.4Hz), 6.94(1H,d,J=3.6Hz), 7.52(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.59(1H,d,J=3.6Hz), 7.68(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.84(1H,s), 7.87(1H,d,J=8Hz), 8.03(1H,d,J=8Hz).

ESI-Mass; 382(MH^+).

Example 166 Synthesis of 3-[2-(tetrahydropyran-4-yl)thiophen-5-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



• 2HCl

In the same manners sequentially as in Examples 161-2 and 20, a yellow compound was obtained (330 mg, yield; 86%) from 4-bromo-2-(tetrahydropyran-4-yl)thiophene (700 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (300 mg). The resulting compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 251-253°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 1.62-1.74(m,2H), 1.94(br,1H), 3.06-3.16(m,2H), 3.18-3.26(m,2H), 3.30-3.38(m,2H), 3.42-3.52(m,4H), 3.61(d,J=11.6Hz,2H), 3.94(d,J=14.0Hz,4H), 6.96(d,J=4.0Hz,1H), 7.56(t,J=8.0Hz,1H), 7.64(t,J=4.0Hz,1H), 7.72(d,J=8.0Hz,1H), 7.89(s,1H), 7.91(d,J=8.0Hz,1H), 8.07(d,J=8.0Hz,1H).

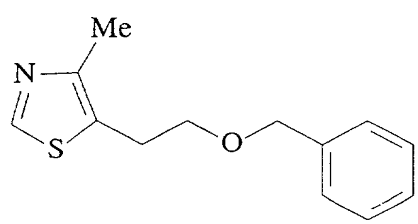
MS(FAB) m/z 408(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 1.83-2.05(m,4H), 2.55(q,J=7.2Hz,2H), 2.74(t,J=4.4Hz,4H), 3.05-3.10(m,1H), 3.51-3.58(m,6H), 4.06-4.09(m,2H), 6.83(dd,J=3.6,0.4Hz,1H), 7.40(ddd,J=8.4,8.0,1.2Hz,1H), 7.48(d,J=3.6Hz,1H), 7.49(s,1H), 7.55(ddd,J=8.4,8.0,1.2Hz,1H), 7.72(d,J=8.0Hz,1H), 8.02(d,J=8.0Hz,1H).

Example 167 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[4-methyl-5-(2-hydroxyethyl)thiazol-2-yl]isoquinoline dihydrochloride

(167-1) 4-Methyl-5-(2-benzyloxyethyl)thiazole

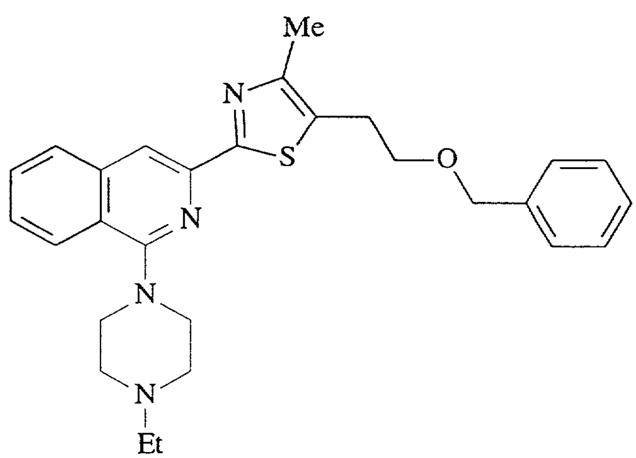


2-(4-Methyl-5-thiazolyl)ethanol (25.71 g) was dissolved in tetrahydrofuran (200 ml), followed by the addition of 60% sodium hydride (7.185 g) under ice-cooling. The resulting mixture was stirred at room temperature for 1 hr. Thereafter,

the it was ice-cooled again, followed by the addition of benzyl bromide (21.4 ml) and tetrabutylammonium bromide (665 mg). The resulting mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a yellow oil (39.059 g, yield; 93%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 2.40(3H,s), 3.06(2H,t,J=6.6Hz), 3.66(2H,t,J=6.6Hz), 4.54(1H,s), 7.26-7.37(5H,m), 8.57(1H,s).

(167-2) 1-(1-Ethylpiperazin-4-yl)-3-[4-methyl-5-(2-benzyloxyethyl)thiazol-2-yl]isoquinoline

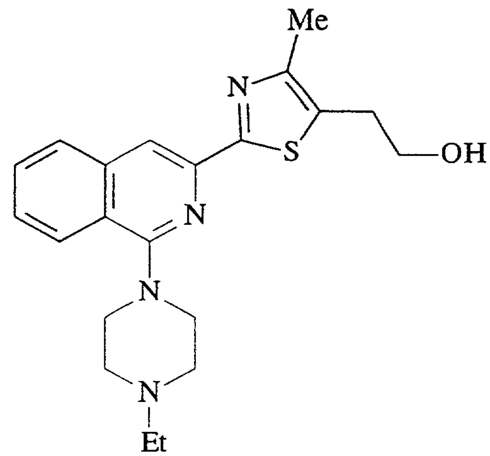


4-Methyl-5-(2-benzyloxyethyl)thiazole (2.333 g) was dissolved in tetrahydrofuran (20 ml), followed by the addition of 2.5 M n-butyl lithium (4 ml) in nitrogen atmosphere at -78°C, and the resulting mixture was stirred for 50 min. Tributyltin chloride (2.8 ml) was added thereto, and the mixture

was stirred for 1 hr. Sequentially, it was stirred at room temperature for 30 min. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was dissolved in xylene (30 ml), followed by the addition of 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (506 mg) and tetrakis(triphenylphosphine)palladium (121 mg), and the resulting mixture was heated under stirring in nitrogen atmosphere at 120°C overnight. The reaction solution was diluted with ethyl acetate and extracted with 2N hydrochloric acid. The resulting aqueous layer was washed with ethyl acetate, basified with 8N sodium hydroxide, and then extracted with ethyl acetate. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/acetone system), to give the title compound as a yellow oil (512 mg, yield; 69%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(3H,t,J=7.2Hz), 2.44(3H,s), 2.54(2H,q,J=7.2Hz), 2.74(4H,t,J=4.4Hz), 3.10(2H,t,J=6.6Hz), 3.57(4H,t,J=4.4Hz), 3.57(4H,t,J=4.4Hz), 3.72(2H,t,J=6.6Hz), 4.57(2H,s), 7.26-7.38(5H,m), 7.47(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.58(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.82(1H,dd,J=8Hz,1.2Hz), 8.04(1H,s), 8.05(1H,dd,J=8Hz,1.2Hz).

(167-3) 1-(1-Ethylpiperazin-4-yl)-3-[4-methyl-5-(2-hydroxyethyl)thiazol-2-yl]isoquinoline dihydrochloride



1-(1-Ethylpiperazin-4-yl)-3-[4-methyl-5-(2-benzyloxyethyl)thiazol-2-yl]isoquinoline (512 mg) was converted into a hydrochloride, which was then dissolved in ethanol (7 ml), followed by the addition of palladium hydroxide (222 mg), and the mixture was stirred in hydrogen atmosphere at room temperature for 3 days. After palladium hydroxide was filtered off, the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system). The resulting product was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/isopropyl ether, to give the hydrochloride of the title compound as pale yellow crystals (129 mg, yield; 27%).

Hydrochloride:

m.p.; 149-154°C

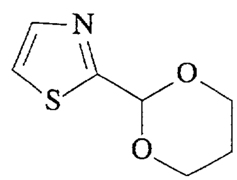
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.30(3H,t,J=7.2Hz), 2.35(3H,s), 2.91(2H,t,J=6.4Hz), 3.15-3.24(2H,m), 3.30(1H,t,J=11.6Hz), 3.33(1H,t,J=11.6Hz), 3.47(2H,t,J=13.2Hz), 3.60(2H,d,J=11.6Hz), 3.60(2H,t,J=6.4Hz), 3.93(2H,d,J=13.2Hz),

7.62(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.74(1H,ddd,J=8Hz,7Hz,1.2Hz), 8.06(1H,d,J=8Hz), 8.10(1H,d,J=8Hz), 8.14(1H,s), 10.92(1H,br-s).

ESI-Mass; 383(MH^+).

Example 168 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(2-hydroxymethylthiazol-5-yl)isoquinoline dihydrochloride

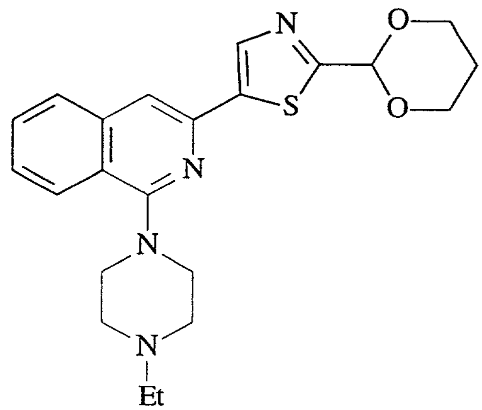
(168-1) 2-(1,3-Dioxan-2-yl)thiazole



2-Thiazolecarboxaldehyde (1 g) was dissolved in toluene (50 ml), followed by the addition of trimethylene glycol (3.36 g) and p-toluenesulfonic acid (17 mg). The resulting mixture was heated under reflux with a Dean-Stark apparatus for 4 hr. After cooling as it was, the reaction mixture was washed sequentially with an aqueous solution of saturated sodium bicarbonate and brine, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a brown solid (1.104 g, yield; 73%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.45-1.53(1H,m), 2.20-2.34(1H,m), 4.00-4.08(2H,m), 4.26-4.34(2H,m), 5.91(1H,s), 7.38(1H,d,J=3.2Hz), 8.01(1H,d,J=3.2Hz).

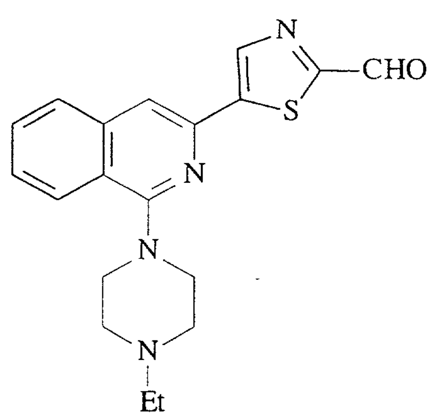
(168-2) 1-(1-Ethylpiperazin-4-yl)-3-[2-(1,3-dioxan-2-yl)thiazol-5-yl]isoquinoline



In the same manner as in Example 167-2, the title compound was obtained as a yellow oil (231 mg, yield; 35%) from 2-(1,3-dioxan-2-yl)thiazole (1.104 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (538 mg).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(3H,t,J=7.2Hz), 1.47-1.53(1H,m), 2.50-2.56(1H,m), 2.54(2H,q,J=7.2Hz), 2.72(4H,t,J=4.8Hz), 3.57(4H,t,J=4.8Hz), 4.02-4.10(2H,m), 4.30-4.36(2H,m), 5.80(2H,s), 7.46(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.57(1H,s), 7.59(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.74(1H,d,J=8Hz), 8.03(1H,d,J=8Hz), 8.25(1H,s).

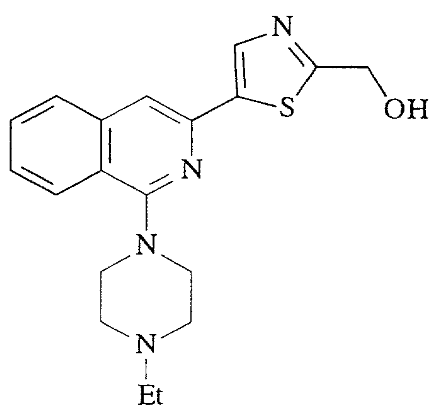
(168-3) 1-(1-Ethylpiperazin-4-yl)-3-(2-formylthiazol-5-yl)isoquinoline



1-(1-Ethylpiperazin-4-yl)-3-[2-(1,3-dioxan-2-yl)thiazol-5-yl]isoquinoline (205 mg) was dissolved in tetrahydrofuran (4 ml), followed by the addition of 1N hydrochloric acid (3 ml), and the resulting mixture was stirred at room temperature for 8 hr. The reaction solution was basified by adding 8N sodium hydroxide thereto, and then extracted with in ethyl acetate. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated, to give the title compound as a colorless oil (155 mg, yield; 80%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(3H,t,J=7.2Hz), 2.55(2H,q,J=7.2Hz), 2.74(4H,t,J=4.8Hz), 3.60(4H,t,J=4.8Hz), 7.53(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.65(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.69(1H,s), 7.81(1H,d,J=8Hz), 8.06(1H,d,J=8Hz), 8.56(1H,s), 9.99(1H,s).

(168-4) 1-(1-Ethylpiperazin-4-yl)-3-(2-hydroxymethylthiazol-5-yl)isoquinoline dihydrochloride



In the same manner as in Example 161, the hydrochloride of the title compound as a yellow amorphous (79 mg, yield; 82%) from 1-(1-ethylpiperazin-4-yl)-3-(2-formylthiazol-5-

yl)isoquinoline (205 mg).

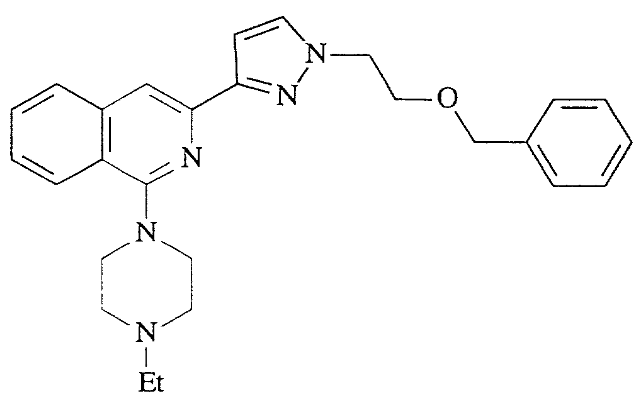
Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.30(3H,t,J=7.2Hz), 3.15-3.23(2H,m), 3.28(1H,t,J=11.6Hz), 3.31(1H,t,J=11.6Hz), 3.49(2H,t,J=13.2Hz), 3.58(2H,d,J=11.6Hz), 3.94(2H,d,J=13.2Hz), 4.73(2H,s), 7.58(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.73(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.90(1H,d,J=8Hz), 7.98(1H,s), 8.07(1H,d,J=8Hz), 8.35(1H,d,J=2Hz), 11.00(1H,br-s).

ESI-Mass; 355(MH^+).

Example 169 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[1-(2-hydroxyethyl)pyrazol-3-yl]isoquinoline dihydrochloride

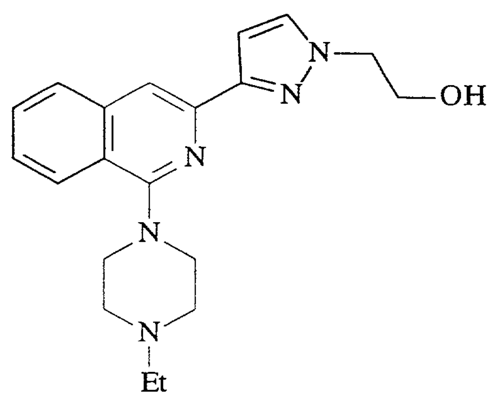
(169-1) 1-(1-Ethylpiperazin-4-yl)-3-[1-(2-benzyloxyethyl)pyrazol-3-yl]isoquinoline



In the same manner as in Example 167-2, the title compound was obtained as a yellow oil (386 mg, yield; 87%) from 1-(2-benzyloxyethyl)-3-bromopyrazole (1.144 g) described in Production Example 42 of JP-A 9-984331 and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (320 mg).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(3H,t,J=7.2Hz), 2.55(2H,q,J=7.2Hz), 2.74(4H,t,J=4.4Hz), 3.53(4H,t,J=4.4Hz), 3.89(2H,t,J=5.4Hz), 4.38(2H,t,J=5.4Hz), 4.51(2H,s), 7.24-7.36(5H,m), 7.38(1H,s), 7.40(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.55(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.70(1H,d,J=8Hz), 8.03(1H,d,J=8Hz), 8.04(1H,s), 8.08(1H,s).

(169-2) 1-(1-Ethylpiperazin-4-yl)-3-[1-(2-hydroxyethyl)pyrazol-3-yl]isoquinoline dihydrochloride



In the same manner as in Example 167, the hydrochloride of the title compound was obtained as pale yellow crystals (340 mg, yield; 92%) from 1-(1-ethylpiperazin-4-yl)-3-[1-(2-benzyloxyethyl)pyrazol-3-yl]isoquinoline (386 mg).

Hydrochloride:

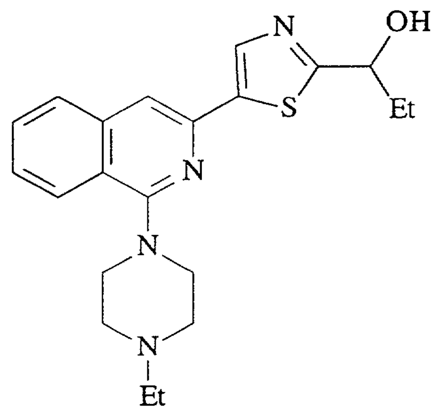
m.p.; 134-140°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.31(3H,t,J=7.2Hz), 3.14-3.25(2H,m), 3.29(1H,t,J=11.2Hz), 3.32(1H,t,J=11.2Hz), 3.49(2H,t,J=13.2Hz), 3.57(2H,d,J=11.2Hz), 3.76(2H,t,J=5.6Hz), 3.91(2H,d,J=13.2Hz), 4.19(2H,t,J=5.6Hz), 7.50(1H,dd,J=8Hz,7Hz), 7.67(1H,dd,J=8Hz,7Hz), 7.70(1H,s),

7.83(1H,d,J=8Hz), 8.03(1H,d,J=8Hz), 8.04(1H,s), 8.26(1H,s).

ESI-Mass; 352(MH^+).

Example 170 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[(1-hydroxypropyl)thiazol-5-yl]isoquinoline dihydrochloride



1-(1-Ethylpiperazin-4-yl)-3-(2-formylthiazol-5-yl)isoquinoline (205 mg) was dissolved in tetrahydrofuran (2 ml), 1M ethylmagnesium bromide/tetrahydrofuran solution (0.26 ml) was added thereto under ice-cooling. The resulting mixture was stirred overnight. An aqueous solution of saturated ammonium chloride was added to the reaction solution, which was then extracted with ethyl acetate. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (toluene/acetone system). The resulting product was converted into a hydrochloride in a conventional manner, and then solidified by adding ether thereto, to give the hydrochloride of the title compound as a brown amorphous (20 mg, yield; 23%).

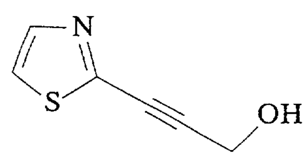
Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.91(3H,t,J=7.6Hz), 1.29(3H,t,J=7.2Hz), 1.68-1.92(2H,m), 3.15-3.23(2H,m), 3.28(1H,t,J=11.6Hz), 3.31(1H,t,J=11.6Hz), 3.48(2H,t,J=13.6Hz), 3.58(2H,d,J=11.6Hz), 3.94(2H,d,J=13.6Hz), 4.71-4.75(1H,m), 7.58(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.73(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.90(1H,d,J=8Hz), 7.97(1H,s), 8.07(1H,d,J=8Hz), 8.33(1H,s), 10.95(1H,br-s).

ESI-Mass; 383(MH^+).

<u>Example 171 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(3-hydroxypropyl)thiazol-5-yl]isoquinoline oxalate</u>

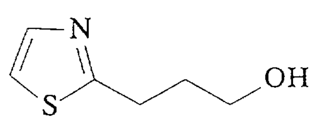
<u>(171-1) 2-(2-Hydroxy-1-propynyl)thiazole</u>



In the same manner as in Example 139-1, the title compound was obtained as a brown oil (8.596 g, yield; 75%) from 2-bromothiazole (13.547 g) and propargyl alcohol (5 ml).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 4.55(2H,s), 7.36(1H,d,J=3.4Hz), 7.81(1H,d,J=3.4Hz).

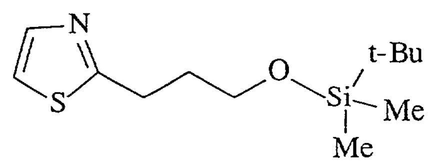
<u>(171-2) 2-(3-Hydroxypropyl)thiazole</u>



In the same manner as in Example 139-2, the title compound was obtained as a yellow oil (2.173 g, yield; 24%) from 2-(3-hydroxy-1-propynyl)thiazole (8.594 g).

^{1}H-NMR(400MHz, $CDCl_3$); δ (ppm) 2.02-2.09(2H,m), 3.18(2H,t,J=7Hz), 3.44(1H,br-s), 3.74(2H,t,J=6Hz), 7.20(1H,d,J=3.4Hz), 7.67(1H,d,J=3.4Hz).

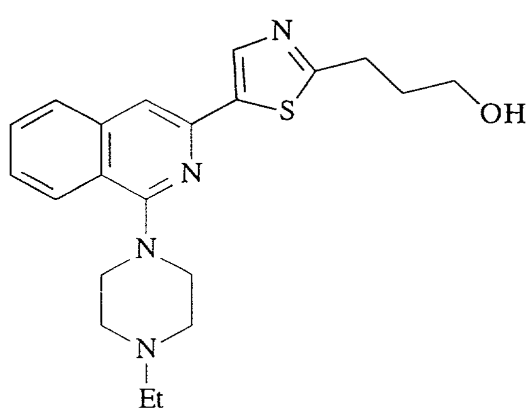
(171-3) 2-[3-(t-Butyldimethylsilyloxy)propyl]thiazole



In the same manner as in Example 163-1, the title compound was obtained as a colorless oil (3.792 g, yield; 98%) from 2-(3-hydroxypropyl)thiazole (2.173 g).

^{1}H-NMR(400MHz, $CDCl_3$); δ (ppm) 0.05(6H,s), 0.90(9H,s), 1.99-2.06(2H,m), 3.11(2H,t,J=7.6Hz), 3.70(2H,t,J=6Hz), 7.19(1H,d,J=3.6Hz), 7.67(1H,d,J=3.6Hz).

(171-4) 1-(1-Ethylpiperazin-4-yl)-3-[2-(3-hydroxypropyl)thiazol-5-yl]isoquinoline oxalate



In the same manner as in Example 167-2, the oxalate of the title compound was obtained as a pale yellow amorphous (221 mg, yield; 25%) from 2-[3-(t-butyldimethylsilyloxy)propyl]thiazole (3.792 g) and 1-(1-

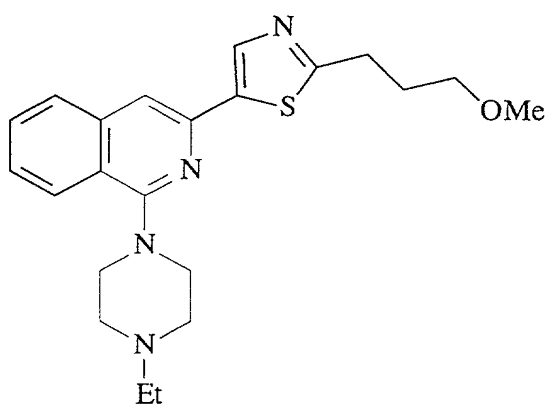
ethylpiperazin-4-yl)-3-bromoisoquinoline (631 mg).

Oxalate:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.23(3H,t,J=7.2Hz), 1.84-1.93(2H,m), 3.02(2H,t,J=7.6Hz), 3.10(2H,q,J=7.2Hz), 3.28-3.38(4H,m), 3.48(2H,t,J=6.4Hz), 3.54-3.70(4H,m), 7.58(1H,dd,J=8Hz,7Hz), 7.90(1H,d,J=8Hz), 7.94(1H,s), 8.07(1H,d,8Hz), 8.29(1H,s).

ESI-Mass; 383(MH^+).

Example 172 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(3-methoxypropyl)thiazol-5-yl]isoquinoline oxalate



1-(1-Ethylpiperazin-4-yl)-3-[2-(3-hydroxypropyl)thiazol-5-yl]isoquinoline (95 mg) was dissolved in tetrahydrofuran (1 ml), followed by the addition of 60% sodium hydride (10 ml) under ice-cooling. The resulting mixture was stirred at room temperature for 40 min. The reaction solution was ice-cooled again, followed by the addition of methyl iodide (17 ml), and the resulting mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The

resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by (NH) silica gel column chromatography (ethyl acetate/hexane system). Then, the resulting product was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as a colorless amorphous (12 mg, yield; 10%).

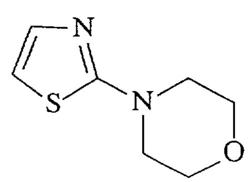
Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.22(3H,t,J=7.2Hz), 1.93-2.00(2H,m), 3.02(2H,t,J=7.6Hz), 3.07(2H,q,J=7.2Hz), 3.24(3H,s), 3.25-3.36(4H,br-s), 3.39(2H,t,J=6.4Hz), 7.58(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.73(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.91(1H,d,J=8Hz), 7.94(1H,s), 8.07(1H,d,J=8Hz), 8.30(1H,s).

ESI-Mass; 397(MH^+).

Example 173 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(4-morpholinyl)-5-thiazolyl]isoquinoline dihydrochloride

(173-1) 2-(4-Morpholinyl)thiazole

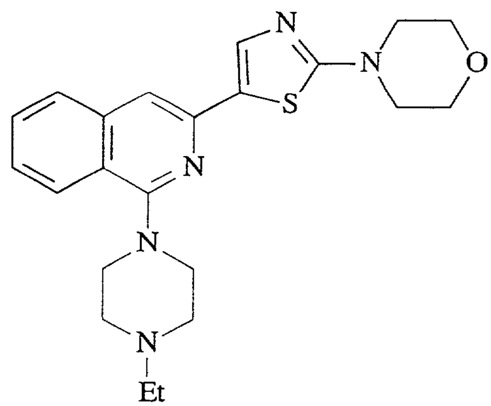


2-Bromothiazole (4.592 g) was added to morpholine (24 ml), and the mixture was stirred at 100°C for 4 hr. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a pale yellow oil (4.531 g, yield;

95%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 3.47(4H,t,J=4.8Hz), 3.83(4H,t,J=4.8Hz), 3.61(2H,d,J=3.8Hz), 7.22(2H,d,J=3.8Hz).

(173-2) 1-(1-Ethylpiperazin-4-yl)-3-[2-(4-morpholinyl)-5-thiazolyl]isoquinoline dihydrochloride



In the same manner as in Example 167-2, the hydrochloride of the title compound was obtained as colorless crystals (recrystallized in ethanol/isopropyl ether) (728 mg, yield; 97%) from 2-(4-morpholinyl)thiazole (1.702 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (543 mg).

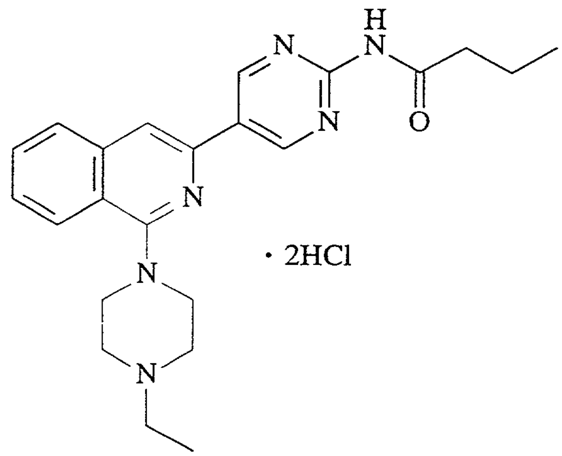
Hydrochloride:

m.p.; 265°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.31(3H,t,J=7.2Hz), 3.18(1H,q,J=7.2Hz), 3.20(1H,q,J=7.2Hz), 3.28(1H,t,J=11.2Hz), 3.31(1H,t,J=11.2Hz), 3.46(2H,t,J=13.2Hz), 3.56(4H,t,J=4.8Hz), 3.57(2H,d,J=11.2Hz), 3.75(4H,t,J=4.8Hz), 3.89(2H,d,J=13.2Hz), 7.55(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.71(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.84(1H,dd,J=8Hz,1.2Hz), 7.89(1H,s), 8.04(1H,s), 8.05(1H,dd,J=8Hz,1.2Hz), 11.40(1H,br-s).

ESI-Mass; 410(MH^+).

Example 174 Synthesis of 3-(2-propylcarbonylaminopyrimidin-5-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (60 mg, yield; 13%) from 5-bromo-2-propylcarbonylaminopyridine (2.73 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (363 mg). The resulting free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 216-219°C

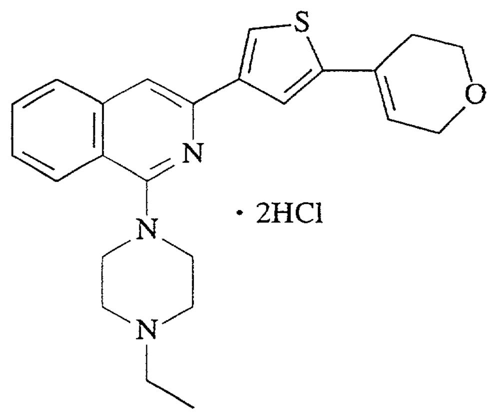
MS(FAB) m/z 405($M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.06(t,J=7.2Hz,3H), 1.17(t,J=7.6Hz,3H), 1.77-1.86(m,2H), 2.55(q,J=7.2Hz,2H), 2.74(br,6H), 3.60(br,4H), 7.51(d,J=8.0,1.2Hz,1H), 7.63(dt,J=8.0,1.2Hz,1H), 7.63(s,1H), 7.81(d,J=8.0Hz,1H),

8.08(d,J=8.0Hz,1H), 9.32(s,2H).

Example 175 Synthesis of 3-[2-(5,6-dihydro-2H-pyran-4-yl)thiophen-4-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, a yellow compound was obtained (310 mg, yield; 82%) from 4-bromo-2-(5,6-dihydro-2H-pyran-4-yl)thiophene (650 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (300 mg). The resulting compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 190-193°C

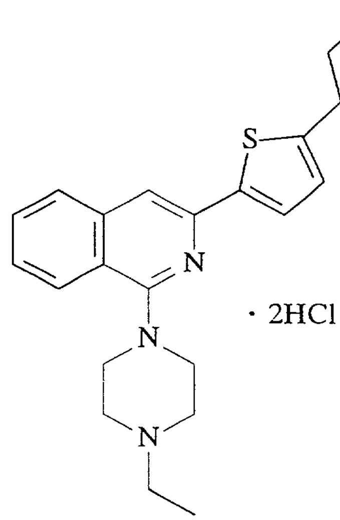
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.32(t,J=7.2Hz,3H), 3.20-3.28(m,2H), 3.30-3.38(m,2H), 3.45-3.52(m,2H), 3.59-3.63(m,2H), 3.83-3.87(m,2H), 3.96-4.02(m,4H), 4.23(d,J=2.8Hz,2H), 6.23(s,1H), 7.59(t,J=8.0Hz,1H), 7.74(t,J=8.0Hz,1H), 7.78(s,1H), 7.91(d,J=8.0Hz,1H), 7.95(s,1H), 8.05(s,1H), 8.09(d,J=8.0Hz,1H).

MS(FAB) m/z 406$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.25(q,J=7.2Hz,2H), 2.61-2.63(m,2H), 2.75(br,4H), 3.56(br,4H), 3.94-3.97(m,2H), 4.32-4.34(m,2H), 6.17(br,1H), 7.44(t,J=8.4Hz,1H), 7.50(s,1H), 7.57(t,J=8.4Hz,1H), 7.58(s,1H), 7.75(d,J=8.4Hz,1H), 7.84(s,1H), 8.05(d,J=8.4Hz,1H).

Example 176 Synthesis of 3-[2-(5,6-dihydro-2H-pyran-4-yl)thiophen-5-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, a yellow compound was obtained (120 mg, yield; 32%) from 5-bromo-2-(5,6-dihydro-2H-pyran-4-yl)thiophene (632 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (300 mg). The resulting compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title

compound as yellow crystals.

Hydrochloride:

m.p.; 256-258°C

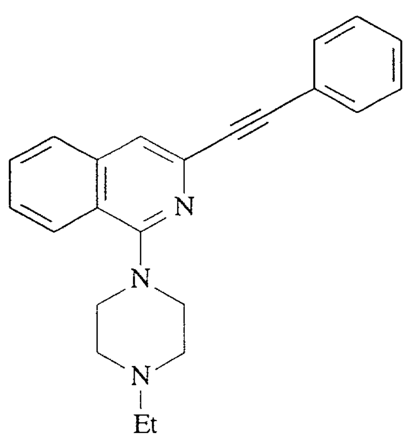
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.32(t,J=7.2Hz,3H), 3.23(br,2H), 3.33(br,4H), 3.48(br,2H), 3.61(br,2H), 3.83(t,J=6.4Hz,2H), 3.96(d,J=13.2Hz,2H), 4.23(br,2H), 6.25(br,1H), 7.16(d,J=3.6Hz,1H), 7.57(t,J=8.0Hz,1H), 7.71(d,J=3.6Hz,1H), 7.73(t,J=8.0Hz,1H), 7.92(d,J=8.0Hz,1H), 7.92(d,J=8.0Hz,1H), 7.95(s,1H), 8.08(d,J=8.0Hz,1H).

MS(FAB) m/z 406$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.52-2.57(m,2H), 2.54(q,J=7.2Hz,2H), 2.74(br,4H), 3.57(br,4H), 3.94(t,J=5.6Hz,2H), 4.40(q,J=2.8Hz,2H), 6.21(br,1H), 6.99(d,J=3.6Hz,1H), 7.42(ddd,J=8.4,8.0,1.2Hz,1H), 7.52(s,1H), 7.53(d,J=3.6Hz,1H), 7.56(ddd,J=8.4,8.0,1.2Hz,1H), 7.72(d,J=8.0Hz,1H), 8.03(d,J=8.4Hz,1H).

<u>Example 177 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(phenylethynyl)isoquinoline dihydrochloride</u>



1-(1-Ethylpiperazin-4-yl)-3-bromoisoquinoline (357 mg) was dissolved in triethylamine (6 ml), followed by the addition of phenylacetylene (132 ml), copper iodide (4 mg) and bis(triphenylphosphine)palladium (II) chloride (14 mg), and the resulting mixture was stirred in nitrogen atmosphere at room temperature overnight, and then stirred at 50°C for 6 hr. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by (NH) silica gel column chromatography (ethyl acetate/hexane system). The resulting product was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/isopropyl ether, to give the hydrochloride of the title compound as yellow crystals (270 mg, yield; 58%).

Hydrochloride:

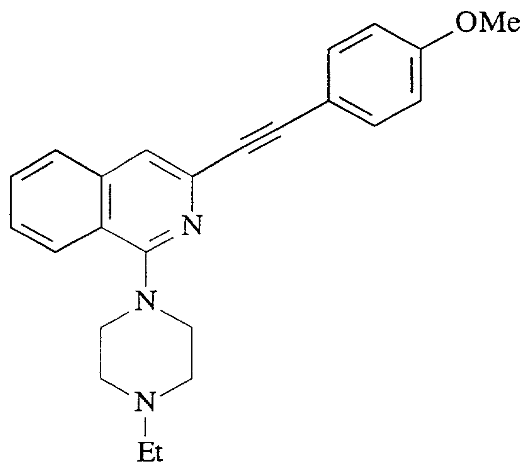
m.p.; 133-136°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.31(3H,t,J=7.2Hz), 3.19(1H,q,J=7.2Hz), 3.20(1H,q,J=7.2Hz), 3.29(1H,t,J=11.2Hz), 3.32(1H,t,J=11.2Hz), 3.49(2H,t,J=13.6Hz), 3.57(2H,d,J=11.2Hz), 3.85(2H,d,J=13.6Hz), 7.42-7.47(3H.m), 7.59-7.63(2H,m), 7.66(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.77(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.83(1H,s), 7.95(1H,d,J=8Hz), 8.12(1H,d,J=8Hz), 11.35(1H,br-s).

ESI-Mass; 342(MH^+).

<u>Example 178 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(4-</u>

methoxyphenyl)ethynylisoquinoline dihydrochloride



In the same manner as in Example 177, the hydrochloride of the title compound was obtained as yellow crystals (recrystallized from ethanol/isopropyl ether) (437 mg, yield; 77%) from 4-methoxyphenylacetylene (185 mg) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (370 mg).

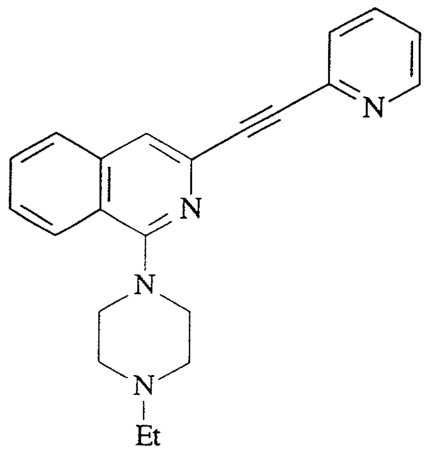
Hydrochloride:

m.p.; 230°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.30(3H,t,J=7.2Hz), 3.20(1H,q,J=7.2Hz), 3.22(1H,q,J=7.2Hz), 3.29(1H,t,J=11.6Hz), 3.32(1H,t,J=11.6Hz), 3.42(2H,t,J=12.8Hz), 3.58(2H,d,J=11.6Hz), 3.80(3H,s), 3.86(2H,d,J=12.8Hz), 7.00(2H,d,J=8.8Hz), 7.55(2H,d,J=8.8Hz), 7.65(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.76(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.78(1H,s), 7.93(1H,d,J=8Hz), 8.11(1H,d,J=8Hz).

ESI-Mass; 372(MH^+).

Example 179 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(2-pyridyl)ethynylisoquinoline oxalate



In the same manner as in Example 177, the oxalate of the title compound was obtained as a yellow amorphous (437 mg, yield; 77%) from 2-ethynylpyridine (157 mg) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (425 mg).

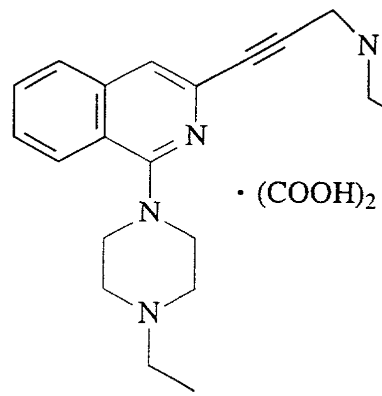
Hydrochloride:

m.p.; 148-154°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.23(3H,t,J=7.2H),
3.10(2H,q,J=7.2Hz), 3.27-3.38(4H,br-s), 3.50-3.66(4H,br-s),
7.44(1H,ddd,J=7.8Hz,4.8Hz,1.2Hz),
7.68(1H,ddd,J=8Hz,7Hz,1.2Hz),
7.70(1H,ddd,J=7.8Hz,1.2Hz,0.8Hz),
7.78(1H,ddd,J=8Hz,7Hz,1.2Hz),
7.7(1H,ddd,J=7.8Hz,7.8H,1.6Hz), 7.96(1H,d,J=8Hz),
8.10(1H,d,J=8Hz), 8.63(1H,ddd,J=4.8Hz,1.6Hz,0.8Hz).

ESI-Mass; 343(MH$^+$).

Example 180 Synthesis of 3-[3-(4-morpholinyl)-1-propynyl]-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



In the same manner as in Example 177, the free compound of the title compound was obtained (485 mg, yield; 77%) from 4-propargyl morpholine (819 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (552 mg). The resulting free compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as yellow crystals.

Oxalate:

m.p.; 231-233°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.28(t,J=7.2Hz,3H), 2.66(t,J=4.8Hz,2H), 3.23(q,J=7.2Hz,2H), 3.46(br,6H), 3.66-3.69(m,8H), 7.66(ddd,J=8.4,8.0,1.2Hz,1H), 7.73(s,1H), 7.77(ddd,J=8.4,8.0,1.2Hz,1H), 7.94(d,J=8.0Hz,1H), 8.12(d,J=8.4Hz,1H).

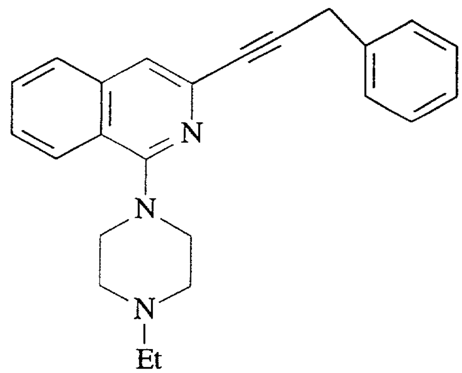
MS(FAB) m/z 365(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.15-1.18(m,3H), 2.57(br,2H), 2.69(t,J=4.8Hz,4H), 2.74(br,4H), 3.51(t,J=4.8Hz,4H), 3.59(s,2H), 3.79(t,J=4.8Hz,4H), 7.45(s,1H),

7.49(ddd,J=8.4,8.0,1.2Hz,1H), 7.60(ddd,J=8.4,8.0,1.2Hz,1H), 7.68(d,J=8.0Hz,1H), 8.03(d,J=8.4Hz,1H).

Example 181 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(3-phenyl-1-propynyl)isoquinoline oxalate



In the same manner as in Example 177, the oxalate of the title compound was obtained as brown crystals (recrystallized from ethanol/isopropyl ether) (468 mg, yield; 73%) from 3-phenyl-1-propyne (268 mg) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (493 mg).

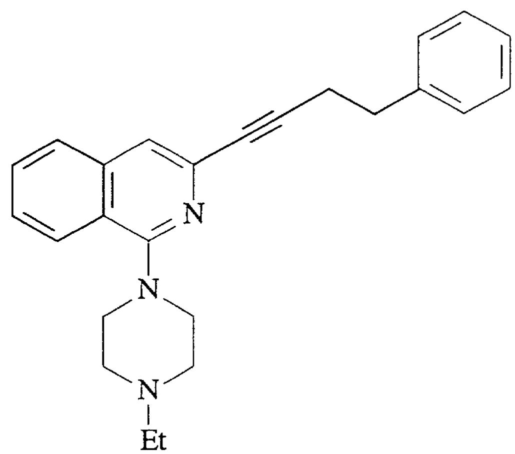
Oxalate:

m.p.; 180-183°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.22(3H,t,J=7.2Hz), 3.09(2H,q,J=7.2Hz), 3.26-3.36(4H,m), 3.46-3.58(4H,m), 3.94(2H,s), 7.23-7.29(1H,m), 7.33-7.44(4H,m), 7.62(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.67(1H,s), 7.73(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.88(1H,d,J=8Hz), 8.07(1H,d,J=8Hz).

ESI-Mass; 356(MH^+).

Example 182 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(4-phenyl-1-butynyl)isoquinoline dihydrochloride



In the same manner as in Example 177, the hydrochloride of the title compound was obtained as brown crystals (recrystallized from ethanol/isopropyl ether) (468 mg, yield; 73%) from 4-phenyl-1-butyne (302 mg) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (474 mg).

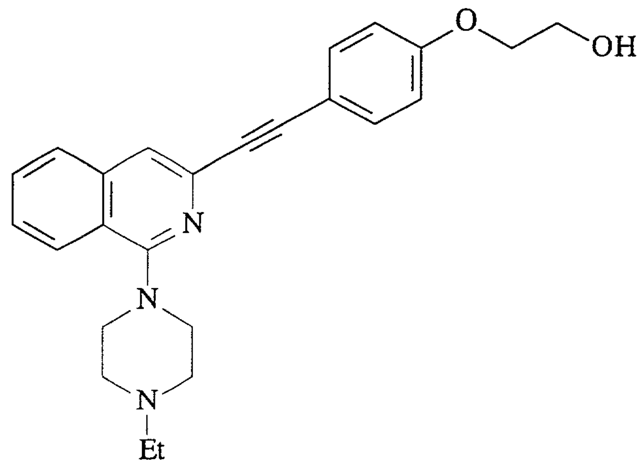
Hydrochloride:

m.p.; 120-128°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.30(3H,t,J=7.2Hz), 2.75(3H,t,J=7.4Hz), 2.88(2H,t,J=7.4Hz), 3.18(1H,q,J=7.2Hz), 3.20(1H,q,J=7.2Hz), 3.26(1H,t,J=11.6Hz), 3.29(1H,t,J=11.6Hz), 3.40(2H,t,J=13.2Hz), 3.56(2H,d,J=11.6Hz), 3.81(2H,d,J=13.2Hz), 7.19-7.23(1H,m), 7.28-7.34(4H,m), 7.56(1H,s), 7.61(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.72(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.88(11H,d,J=8Hz), 8.07(1H,d,J=8Hz), 11.00(1H,br-s).

ESI-Mass; 370(MH$^+$).

Example 183 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[4-(2-hydroxyethoxy)phenylethynyl]isoquinoline dihydrochloride



4-Iodophenol (11.041 g) was dissolved in N,N-dimethylformamide (100 ml), followed by the addition of 60% sodium hydride (2.2 g) under ice-cooling, and the mixture was stirred at room temperature for 30 min. Subsequently, the mixture was ice-cooled again, followed by the addition of (2-bromoethoxy)-t-butyldimethylsilane (13.158 g), and the mixture was stirred at room temperature for 2 hr. Then the mixture was stirred at 80°C for further 2 hr. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue and (trimethylsilyl)acetylene (6 g) were treated in the same manner as in Example 139-1. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was dissolved in tetrahydrofuran (50 ml), followed by the addition of 5N hydrochloric acid (25 ml), and the resulting mixture was stirred for 30 min. Then, it was

extracted with ethyl acetate and evaporated. The resulting residue was dissolved in methanol (15 ml), followed by the addition of 1N sodium hydroxide (5 ml), and the mixture was stirred at room temperature for 2 hr. The resulting mixture was evaporated, and the resulting residue was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. From the product obtained by the same treatment as in Example 177 and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (419 mg), the hydrochloride of the title compound was obtained as yellow crystals (recrystallized in ethanol/isopropyl ether) (328 mg, yield; 54%).

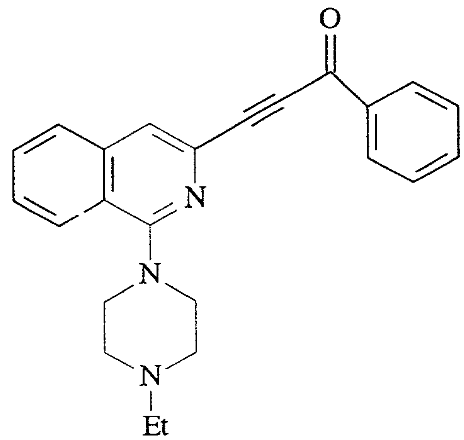
Hydrochloride:

m.p.; 205-208°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.31(3H,t,J=7.2Hz), 3.19(1H,q,J=7.2Hz), 3.21(1H,q,J=7.2Hz), 3.29(1H,t,J=10.8Hz), 3.32(1H,t,J=10.8Hz), 3.45(2H,t,J=13.6Hz), 3.58(2H,d,J=10.8Hz), 3.71(2H,t,J=4.8Hz), 3.85(2H,d,J=13.6Hz), 4.03(2H,t,J=4.8Hz), 7.00(2H,d,J=8.8Hz), 7.54(2H,d,J=8.8Hz), 7.65(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.76(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.78(1H,s), 7.93(1H,d,J=8Hz), 8.11(1H,d,J=8Hz), 11.02(1H,br-s).

ESI-Mass; 402(MH^+).

<u>Example 184 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-benzoylethynylisoquinoline oxalate</u>



1-(1-Ethylpiperazin-4-yl)-3-(3-hydroxy-3-phenyl-1-propynyl)isoquinoline (400 mg) was dissolved in chloroform (30 ml), followed by the addition of manganese dioxide (4.038 g), and the resulting mixture was stirred at room temperature for 1 hr. After the manganese dioxide was filtered off, the resulting solution was evaporated, and the resulting residue was purified by silica gel column chromatography (ethyl acetate/acetone system). The resulting product was converted into an oxalate in a conventional manner, and then recrystallized from ethanol, to give the oxalate of the title compound as brown crystals (358 mg, yield; 73%).

Oxalate:

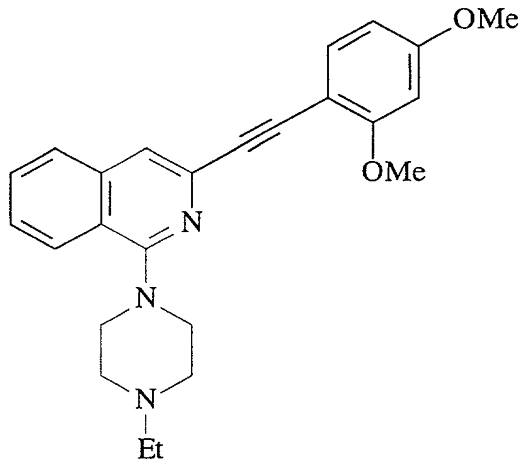
m.p.; 161-163°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.23(3H,t,J=7.2Hz), 3.07(2H,q,J=7.2Hz), 3.25-3.35(4H,m), 3.54-3.68(4H,m), 7.63-7.68(2H,m), 7.74-7.87(3H,m), 8.06(1H,d,J=8Hz), 8.16(1H,d,J=8Hz), 8.19-8.22(3H,m).

ESI-Mass; 370(MH^+).

<u>Example 185 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(2,4-</u>

dimethoxyphenylethynyl)isoquinoline dihydrochloride



1-Bromo-2,4-dimethoxybenzene (2.18 g) was dissolved in triethylamine (20 ml), followed by the addition of (trimethylsilyl)acetylene (1.092 g), copper iodide (38 mg) and bis(triphenylphosphine)palladium (II) chloride (140 mg), and the resulting mixture was stirred in nitrogen atmosphere at 50°C overnight. The resulting insoluble matters were filtered off from the reaction mixture, which was then evaporated. The resulting residue was dissolved in methanol (50 ml), followed by the addition of 1N sodium hydroxide (20 ml), and the mixture was stirred at room temperature for 1 hr. Subsequently, it was evaporated. The resulting residue was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. Then, the resulting residue was dissolved in triethylamine (15 ml), followed by the addition of 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (415 mg), cooper iodide (5 mg) and bis(triphenylphosphine)palladium (II) chloride (18 mg), and

the resulting mixture was stirred in nitrogen atmosphere at 50°C overnight. The resulting insoluble matters were filtered off from the reaction mixture, which was then evaporated. Ethyl acetate was added to the resulting residue, and then the mixture was extracted with 2N hydrochloric acid. The resulting aqueous layer was basified with 8N sodium hydroxide and extracted with ethyl acetate. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by (NH) silica gel column chromatography (ethyl acetate/hexane system). The resulting product was converted into a hydrochloride in a conventional manner, and then recrystallized (from ethanol/isopropyl ether), to give the hydrochloride of the title compound as yellow crystals (161 mg, yield; 31%).

Hydrochloride:

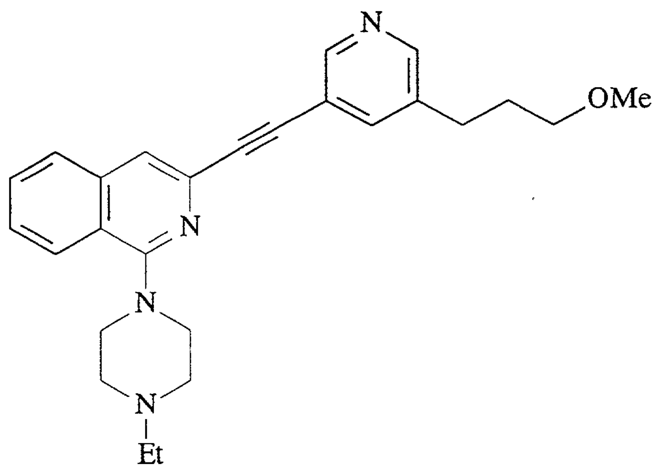
m.p.; 123-129°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.30(3H,t,J=7.2Hz), 3.20(1H,q,J=7.2Hz), 3.22(1H,q,J=7.2Hz), 3.29(1H,t,J=10.8Hz), 3.32(1H,t,J=10.8Hz), 3.42(2H,t,J=12.8Hz), 3.58(2H,d,J=10.8Hz), 3.81(3H,s), 3.82(2H,d,J=12.8Hz), 3.86(3H,s), 6.58(1H,dd,J=8.4Hz.2.4Hz), 7.45(1H,d,J=8.4Hz), 7.63(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.73(1H,s), 7.75(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.93(1H,d,J=8Hz), 8.10(1H,d,J=8Hz), 10.90(1H,br-s).

ESI-Mass; 420(MH^+).

Example 186 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[3-(3-

methoxypropyl)-5-pyridyl]ethynylisoquinoline



In the same manner as in Example 185, the hydrochloride of the title compound was obtained as pale yellow crystals (recrystallized from ethanol/isopropyl ether) (361 mg, yield; 50%) from 5-bromo-3-(3-methoxypropyl)pyridine (470 mg), (trimethylsilyl)acetylene (390 mg) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (345 mg).

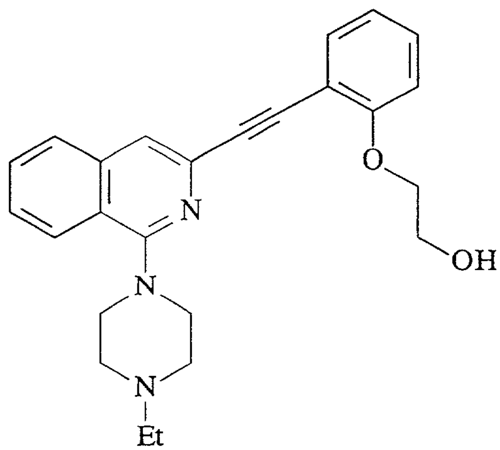
Hydrochloride:

m.p.; 135-140°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.32(3H,t,J=7.2Hz), 1.84-1.92(2H,m), 2.79(2H,t,J=7.8Hz), 3.18(1H,q,J=7.2Hz), 3.20(1H,q,J=7.2Hz), 3.22(3H,s), 3.29(1H,t,J=11.6Hz), 3.32(1H,t,J=11.6Hz), 3.33(2H,t,J=6.2Hz), 3.51(2H,t,J=13.2Hz), 3.57(2H,d,J=11.6Hz), 3.84(2H,d,J=13.2Hz), 7.71(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.80(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.92(1H,s), 7.99(1H,d,J=8Hz), 8:15(1H,d,J=8Hz), 8.47(1H,t,J=2Hz), 8.73(1H,d,J=2Hz), 8.97(1H,d,J=2Hz), 11.60(1H,br-s).

ESI-Mass; 415(MH^+).

<u>Example 187 Synthesis of 1-(1-Ethylpiperazin-4-yl)-3-[2-(2-hydroxyethoxy)phenyl]ethynylisoquinoline oxalate</u>



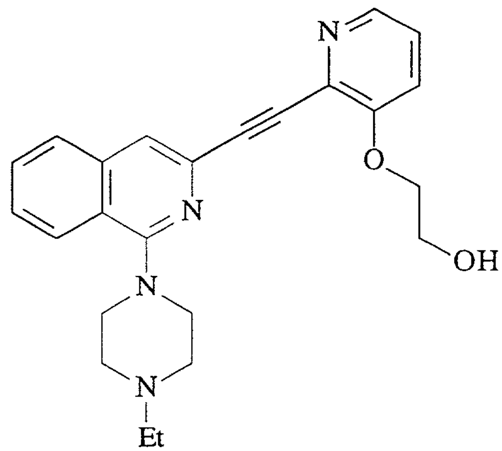
In the same manner as in Example 185, the oxalate of the title compound was obtained as a pale yellow amorphous (330 mg, yield; 54%) from 2-iodophenol (1.089 g), (2-bromoethoxy)-t-butyldimethylsilane (1.302 g), (trimethylsilyl)acetylene (579 mg) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (408 mg).

Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.24(3H,t,J=7.2Hz), 3.11(2H,q,J=7.2Hz), 3.30-3.38(4H,m), 3.33-3.48(1H,m), 3.50-3.66(4H,m), 3.78(2H,t,J=5.2Hz), 4.12(2H,t,J=5.2Hz), 6.98(1H,ddd,J=7.6Hz,7.6Hz,1.6Hz), 7.65(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.75(1H,s), 7.76(1H,ddd,J=8Hz,7Hz,1.2Hz), 7:93(1H,d,J=8Hz), 8.11(1H,d,J=8Hz).

ESI-Mass; 402(MH^+).

Example 188 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[3-(2-hydroxyethoxy)-2-pyridyl]ethynylisoquinoline



In the same manner as in Example 185, the hydrochloride of the title compound was obtained as yellow crystals (261 mg, yield; 38%) from 2-bromo-3-hydroxypyridine (2.095 g), (2-bromoethoxy)-t-butyldimethylsilane (3.425 g), (trimethylsilyl)acetylene (613 mg) and 1-(1-ethylpiperazin-4-yl-3-bromoisoquinoline (410 mg).

Hydrochloride:

m.p.; 153-159°C

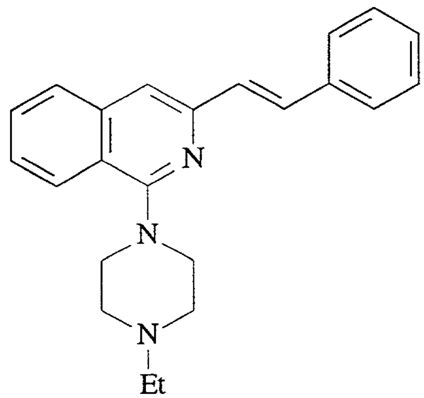
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.31(3H,t,J=7.2Hz), 3.18(1H,q,J=7.2Hz), 3.20(1H,q,J=7.2Hz), 3.29(1H,t,J=10.2Hz), 3.32(1H,t,J=10.2Hz), 3.51(2H,t,J=13.2Hz), 3.58(2H,d,J=10.2Hz), 3.80(1H,t,J=5Hz), 3.90(2H,d,J=13.2Hz), 4.23(1H,t,J=5Hz), 7.55(1H,dd,J=8.4Hz,1.6Hz), 7.89(1H,s), 7.99(1H,d,J=8Hz), 8.13(1H,d,J=8Hz), 8.26(1H,dd,J=4.6Hz,1.6Hz), 7.89(1H,s), 7.99(1H,d,J=8Hz), 8.13(1H,d,J=8Hz), 8.26(1H,dd,J=4.6Hz,1.6Hz), 7.89(1H,s),

7.99(1H,d,J=8Hz), 8.13(1H,d,J=8Hz),

8.26(1H,dd,J=4.6Hz,1.6Hz), 11.55(1H,br-s).

ESI-Mass; 403(MH^+).

Example 189 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(trans-2-phenylethenyl)isoquinoline dihydrochloride



1-(1-Ethylpiperazin-4-yl)-3-bromoisoquinoline (702 mg) was dissolved in N,N-dimethylformamide (15 ml), followed by the addition of styrene (369 mg), palladium (II) acetate (49 mg), tri-o-tolylphosphine (134 mg) and triethylamine (5 ml), and the resulting mixture was stirred in nitrogen atmosphere at 100°C overnight. After the insoluble matters were filtered off, the resulting filtrate was evaporated. The resulting residue was purified by (NH) silica gel column chromatography (ethyl acetate/hexane system). The resulting product was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/isopropyl ether, to give the hydrochloride of the title compound as pale brown crystals (412 mg, yield; 45%).

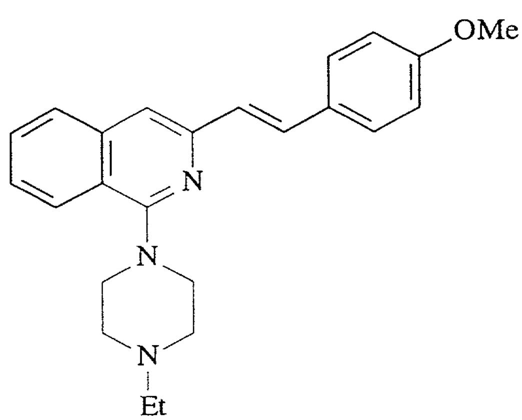
Hydrochloride:

m.p.; 222-225°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.32(3H,t,J=7.2Hz), 3.21(1H,q,J=7.2Hz), 3.23(1H,q,J=7.2Hz), 3.33(1H,t,J=11.2Hz), 3.55(1H,t,J=11.2Hz), 3.49(2H,t,J=13.6Hz), 3.60(2H,d,J=11.2Hz), 3.96(2H,d,J=13.6Hz), 7.27-7.32(1H,m), 7.35(1H,d,J=15.6Hz), 7.40(2H,t,J=7.6Hz), 7.50(1H,s), 7.57(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.65(2H,d,J=7.6Hz), 7.68(1H,d,J=15.6Hz), 7.70(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.89(1H,d,J=8Hz), 10.59(1H,br-s).

ESI-Mass; 344(MH^+).

Example 190 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[trans-2-(4-methoxyphenyl)ethenyl]isoquinoline dihydrochloride



In the same manner as in Example 189, the hydrochloride of the title compound was obtained as yellow crystals (450 mg, yield; 53%) from 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (595 mg) and 4-methoxystyrene (382 mg).

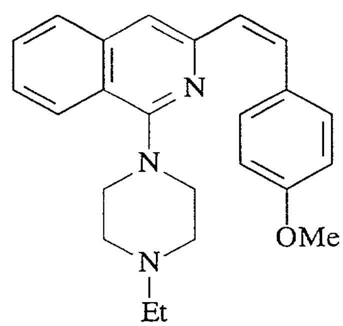
Hydrochloride:

m.p.; 227°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.32(3H,t,J=7.2Hz), 3.20(1H,q,J=7.2Hz), 3.22(1H,q,J=7.2Hz), 3.31(1H,t,J=11.6Hz), 3.34(1H,t,J=11.6Hz), 3.60(2H,d,J=11.6Hz), 3.78(3H,s), 3.95(2H,d,J=13.6Hz), 6.96(2H,d,J=8.8Hz), 7.20(1H,d,J=15.6Hz), 7.45(1H,s), 7.54(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.59(2H,d,J=8.8Hz), 7.63(1H,d,J=15.6Hz), 7.69(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.86(1H,dd,J=8Hz,1.2Hz), 8.06(1H,dd,J=8Hz,1.2Hz), 11.05(1H,br-s).

ESI-Mass; 374(MH^+).

Example 191 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[cis-2-(4-methoxyphenyl)ethenyl]isoquinoline oxalate



1-(1-Ethylpiperazin-4-yl)-3-(4-methoxyphenylethynyl)isoquinoline (226 mg) was dissolved in ethanol (10 ml), followed by the addition of Lindlar catalyst (45 mg), and the resulting mixture was stirred in hydrogen atmosphere at room temperature for 25 min. After the catalyst was filtered off, the mixture was evaporated and partitioned between ethyl acetate and 1N sodium hydroxide. The resulting organic layer was washed with water, dried (over $MgSO_4$), evaporated, and then purified by (NH) silica gel column

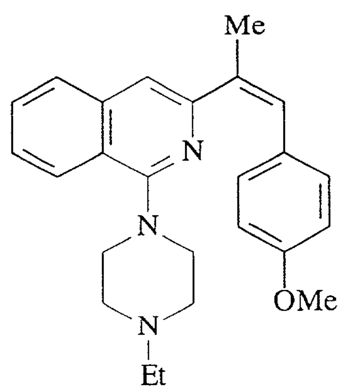
chromatography (ethyl acetate/hexane system). The resulting product was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as a yellow amorphous (137 mg, yield; 49%).

Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.02(3H,t,J=7.2Hz), 2.83(2H,q,J=7.2Hz), 2.94-3.04(4H,m), 3.14-3.28(4H,m), 3.58(3H,s), 6.40(1H,d,J=12.4Hz), 6.48(1H,d,J=12.4Hz), 6.68(1H,d,J=8.8Hz), 7.21(2H,d,J=8.8Hz), 7.22(1H,s), 7.39(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.50(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.63(1H,d,J=8Hz), 7.87(1H,d,J=8Hz).

ESI-Mass; 374(MH^+).

<u>Example 192 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(cis-1-methyl-2-phenylethenyl)isoquinoline oxalate</u>



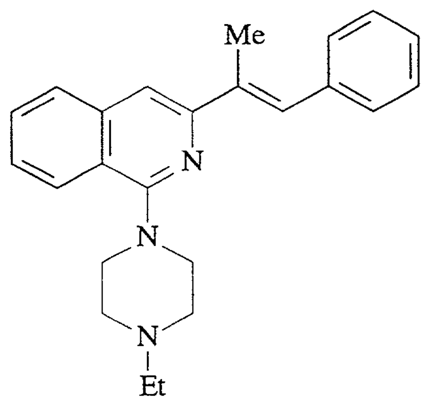
In the same manner as in Example 189, the oxalate of the title compound was obtained as a yellow amorphous (465 mg, yield; 53%) from 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (617 mg) and cis-β-methylstyrene (451 mg).

Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.14(3H,t,J=7.2Hz), 2.25(3H,s), 3.01(2H,q,J=7.2Hz), 3.12-3.22(4H,m), 3.30-3.44(4H,m), 6.64(1H,s), 6.93(2H,d,J=7.6Hz), 7.04-7.12(3H,m), 7.29(1H,s), 7.5(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.64(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.76(1H,d,J=8Hz), 8.03(1H,d,J=8Hz).

ESI-Mass; 358(MH$^+$).

Example 193 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(trans-1-methyl-2-phenylethenyl)isoquinoline



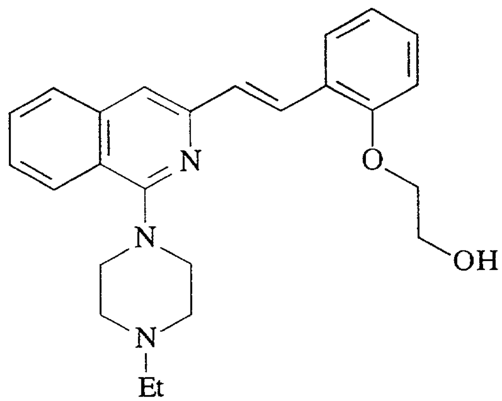
In the same manner as in Example 189, the oxalate of the title compound was obtained as a yellow amorphous (576 mg, yield; 68%) from 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (607 mg) and trans-β-methylstyrene (453 mg).

Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.24(3H,t,J=7.2Hz), 2.31(3H,s), 3.12(2H,q,J=7.2Hz), 3.30-3.40(4H,m), 3.54-3.70(4H,m), 7.25-7.32(1H,m), 7.39-7.45(4H,m), 7.57(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.69(1H,s), 7.70(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.82(1H,s), 7.95(1H,dd,J=8Hz,1.2Hz), 8.08(1H,dd,J=8Hz,1.2Hz).

ESI-Mass; 358(MH$^+$).

Example 194 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[trans-2-(2-hydroxyethoxyphenyl)ethenyl]isoquinoline oxalate



The product obtained from 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (700 mg) and 2-vinylphenoxyacetate n-butyl ester (486 mg) by the same treatment as in Example 189 was dissolved in tetrahydrofuran (6 ml), followed by the addition of lithium aluminium hydride (83 mg) under ice-cooling, and stirring for 5 min. To the reaction mixture were sequentially added water (85 ml), 5N sodium hydroxide (85 ml) and water (255 ml), the resulting insoluble matters were filtered off through Celite, and the resulting solution was evaporated. The resulting residue was purified by (NH) silica gel column chromatography (ethyl acetate/hexane system), and then converted into an oxalate in a conventional manner, to give the oxalate of the title compound as a yellow amorphous (248 mg, yield; 23%).

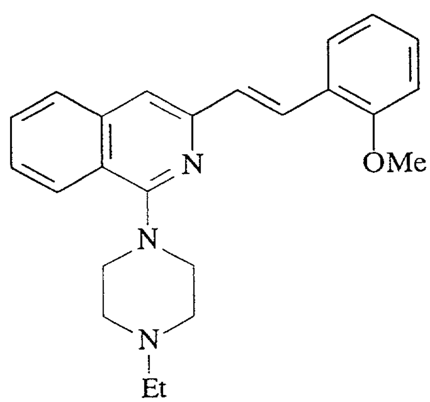
Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.25(3H,t,J=7.2Hz),

3.13(2H,q,J=7.2Hz), 3.30-3.42(4H,m), 3.60-3.80(4H,m), 3.82(2H,t,J=5Hz), 4.08(2H,t,J=5Hz), 6.98(1H,dd,J=7.6Hz,7.6Hz), 7.05(1H,d,J=8.2Hz), 7.26(1H,ddd,J=8.2Hz,7.6Hz,1.6Hz), 7.34(1H,d,J=16Hz), 7.42(1H,s), 7.54(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.68(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.69(1H,dd,J=7.6Hz,1.6Hz), 7.87(1H,d,J=8Hz), 8.06(1H,d,J=16Hz), 8.06(1H,d,J=8Hz).

ESI-Mass; 404(MH^+).

Example 195 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[trans-2-(2-methoxyphenyl)ethenyl]isoquinoline oxalate



In the same manner as in Example 189, the oxalate of the title compound obtained as a yellow amorphous (224 mg, yield; 31%) from 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (507 mg) and 2-methoxystyrene (425 mg).

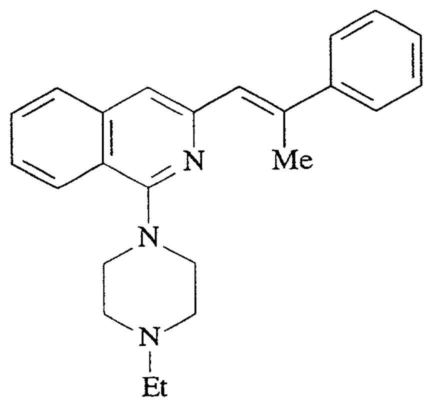
Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.26(3H,t,J=7.2Hz), 3.16(2H,q,J=7.2Hz), 3.36-3.46(4H,m), 3.54-3.72(4H,m), 3.87(3H,s), 6.98(1H,t,J=7.6Hz), 7.06(1H,d,J=8.2Hz), 7.29(1H,ddd,J=8.2Hz,7.6Hz,1.6Hz), 7.30(1H,d,16Hz),

7.47(1H,s), 7.55(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.68(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.69(1H,dd,J=7.6Hz,1.6Hz), 7.88(1H,d,J=8Hz), 7.96(1H,d,J=16Hz), 8.07(1H,d,J=8Hz).

FAB-Mass; 376(MH^+).

Example 196 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(trans-2-methyl-2-phenylethen-1-yl)isoquinoline oxalate



In the same manner as in Example 189, the oxalate of the title compound was obtained as a yellow amorphous (371 mg, yield; 44%) from 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (584 mg) and α-methylstyrene (425 mg).

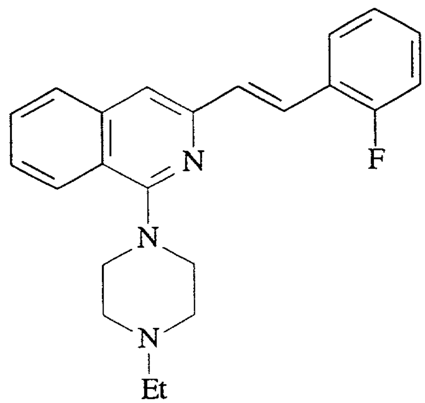
Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.23(3H,t,J=7.2Hz), 2.68(3H,d,J=1.2Hz), 3.08(2H,q,J=7.2Hz), 3.28-3.38(4H,m), 3.50-3.64(4H,m), 6.87(1H,d,J=1.2Hz), 7.28-7.34(1H,m), 7.40(2H,t,J=7.6Hz), 7.52(1H,s), 7.54-7.62(3H,m), 7.69(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.86(1H,d,J=8Hz), 8.08(1H,d,J=8Hz).

FAB-Mass; 368(MH^+).

Example 197 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-

[trans-2-(2-fluorophenyl)ethenyl]isoquinoline oxalate



In the same manner as in Example 189, the oxalate of the title compound was obtained as a yellow amorphous (563 mg, yield; 71%) from 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (542 mg) and 2-fluorostyrene (415 mg).

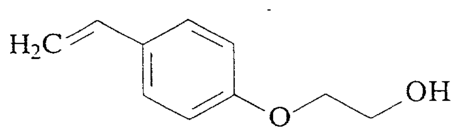
Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.24(3H,t,J=7.2Hz), 3.09(2H,q,J=7.2Hz), 3.25-3.40(4H,m), 3.50-3.70(4H,m), 7.22-7.28(2H,m), 7.31-7.38(1H,m), 7.42(1H,d,J=15.6Hz), 7.53(1H,s), 7.58(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.71(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.81(1H,d,J=15.6Hz), 7.82-7.87(1H,m), 7.90(1H,dd,J=8Hz,1.2Hz), 8.08(1H,dd,J=8Hz,1.2Hz).

FAB-Mass; 362(MH^+).

Example 198 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[(E)-4-(2-hydroxyethoxy)styryl]isoquinoline oxalate

(198-1) 2-(4-Vinylphenoxy)ethanol

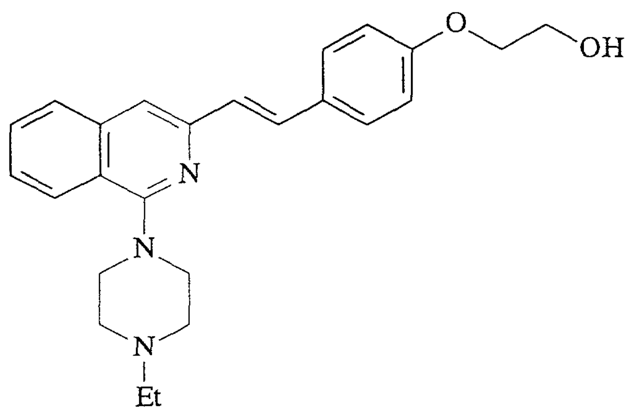


4-Hydroxybenzaldehyde (3.664 g) was dissolved in N, N-dimethylformamide (60 ml), followed by the addition of 60% sodium hydride (1.44 g) under ice-cooling. The resulting mixture was stirred at room temperature for 40 min. To the mixture was added (2-bromoethoxy)-t-butyldimethylsilane (8.612 g), and the resulting mixture was stirred at 100°C for 30 min. After the mixture was cooled as it was, it was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was dissolved in N,N-dimethylformamide (70 ml), followed by the addition of (ethyl)triphenylphosphonium bromide (13.218 g) and 60% sodium hydride (1.623 g) under ice-cooling, and the resulting mixture was stirred at room temperature for 2 hr. Water was added to the reaction mixture, extracted with hexane extraction, and then the resulting organic layer was evaporated. The resulting residue was dissolved in tetrahydrofuran (50 ml), followed by the addition of 2N hydrochloric acid (20 ml) and stirring for 1 hr. The reaction mixture was extracted with ethyl acetate, and the resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a colorless solid (3.025 g, yield; 60%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 2.09(1H,s), 3.97(2H,t,J=4.6Hz), 4.09(2H,t,J=4.6Hz), 5.14(1H,dd,J=10.8Hz,0.8Hz),

5.62(1H,dd,J=17.6Hz,0.8Hz), 6.68(1H,dd,J=17.6Hz,10.8Hz), 6.83(1H,ddd,J=8Hz,2.4Hz,0.8Hz), 6.97(1H,dd,J=2.4Hz,1.6Hz), 7.03(1H,ddd,J=8Hz,1.6Hz,0.8Hz), 7.25(1H,t,J=8Hz).

(198-2) 1-(1-Ethylpiperazin-4-yl)-3-[(E)-4-(2-hydroxyethoxy)styryl]isoquinoline oxalate



In the same manner as in Example 189, the oxalate of the title compound was obtained as a yellow amorphous (788 mg, yield; 89%) from 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (580 mg) and 2-(4-vinylphenoxy)ethanol (534 mg).

Oxalate:

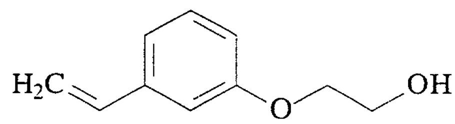
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.25(3H,t,J=7.2Hz), 3.13(2H,q,J=7.2Hz), 3.30-3.42(4H,m), 3.54-3.72(4H,m), 3.71(2H,t,J=5Hz), 4.01(2H,t,J=5Hz), 6.96(2H,d,J=8.8Hz), 7.18(1H,d,J=15.6Hz), 7.42(1H,s), 7.54(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.57(2H,d,J=8.8Hz), 7.62(1H,d,J=15.6Hz), 7.68(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.85(1H,d,J=8Hz), 8.06(1H,d,J=8Hz).

FAB-Mass; 404(MH^+).

Example 199 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-

{trans-2-[3-(2-hydroxyethoxy)phenyl]ethenyl}isoquinoline oxalate

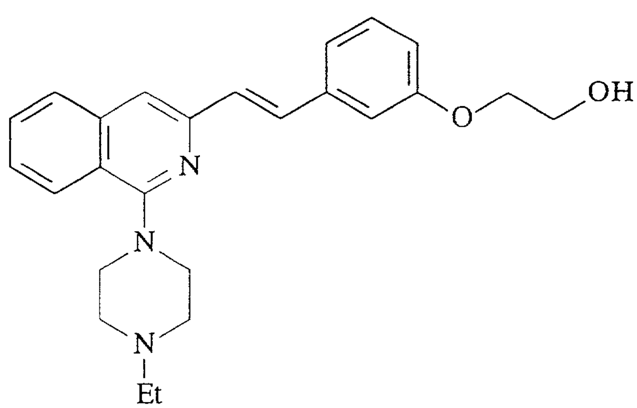
(199-1) 2-(3-Vinylphenoxy)ethanol



In the same manner as in Example 198-1, the title compound was obtained as a colorless oil (2.931 g, yield; 60%) from 3-hydroxybenzaldehyde (3.664 g), (2-bromoethoxy)-t-butyldimethylsilane (8.612 g) and (ethyl)triphenylphosphonium bromide (13.240 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 2.00-2.03(1H,m), 3.95-4.00(2H,m), 4.11(2H,t,J=4.6Hz), 5.26(1H,dd,J=10.8Hz,0.8Hz), 5.74(1H,dd,J=17.6Hz,0.8Hz), 6.68(1H,dd,J=17.6Hz,10.8Hz), 6.83(1H,ddd,J=8Hz,2.4Hz,0.8Hz), 6.97(1H,dd,J=2.4Hz,1.6Hz), 7.03(1H,ddd,J=8Hz,1.6Hz,0.8Hz), 7.25(1H,t,J=8Hz).

(199-2) 1-(1-Ethylpiperazin-4-yl)-3-[trans-2-[3-(2-hydroxyethoxy)phenyl]ethenyl]isoquinoline oxalate



In the same manner as in Example 189, the oxalate of the title

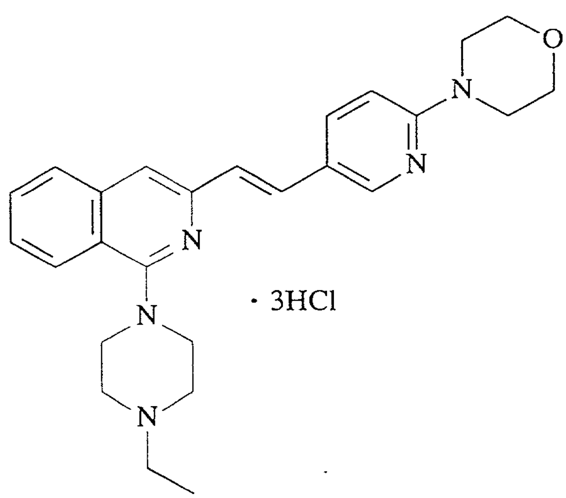
compound was obtained as a yellow amorphous (571 mg, yield; 71%) from 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (560 mg) and 2-(3-vinylphenoxy)ethanol (504 mg).

Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.25(3H,t,J=7.2Hz), 3.15(2H,q,J=7.2Hz), 3.32-3.44(4H,m), 3.52-3.74(4H,m), 3.73(2H,t,J=5Hz), 4.04(2H,t,J=5Hz), 6.87(1H,dd,J=8Hz,2.4Hz), 7.20(1H,d,J=7.6Hz), 7.22(1H,d,J=2.4Hz), 7.29(1H,dd,J=8Hz,7.6Hz), 7.35(1H,d,J=15.6Hz), 7.48(1H,s), 7.56(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.64(1H,d,J=15.6Hz), 7.70(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.87(1H,d,J=8Hz), 8.07(1H,d,J=8Hz).

FAB-Mass; 404(MH$^+$).

Example 200 Synthesis of 3-{(E)-2-[2-(4-morpholinyl)pyridin-5-yl]ethenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manner as in Example 189, the free compound of the title compound was obtained (1.06 g, yield; 95%) from

2-(4-morpholinyl)-5-vinylpyridine (1.0 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (832 mg). The resulting free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 190-194°C

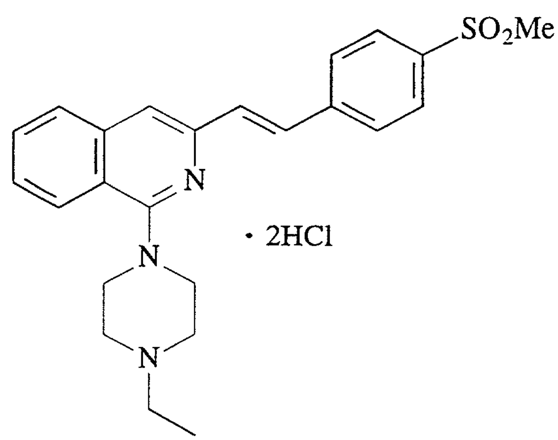
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.35(t,J=7.2Hz,3H), 3.18-3.26(m,2H), 3.30-3.39(m,2H), 3.52-3.62(m,4H), 3.78(br,8H), 3.99(d,J=13.2Hz,2H), 7.44(d,J=16.0Hz,1H), 7.46(d,J=9.6Hz,1H), 7.49(s,1H), 7.60(t,J=8.0Hz,1H), 7.68(d,J=16.0Hz,1H), 7.73(t,J=8.0Hz,1H), 7.91(d,J=8.0Hz,1H), 8.09(d,J=8.0Hz,1H), 8.28(d,J=2.0Hz,1H), 8.47(d,J=9.6Hz,1H).

MS(FAB) m/z 422(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.76(br,4H), 3.56(t,J=4.8Hz,8H), 3.84(t,J=4.8Hz,4H), 6.66(d,J=8.8Hz,1H), 7.02(d,J=15.6Hz,1H), 7.16(s,1H), 7.42(ddd,J=8.4,8.0,1.2Hz,1H), 7.55(ddd,J=8.4,8.0,1.2Hz,1H), 7.67(d,J=8.0Hz,1H), 7.68(d,J=15.6Hz,1H), 7.80(dd,J=8.8,2.4Hz,1H), 8.04(d,J=8.4Hz,1H), 8.37(d,J=2.4Hz,1H).

Example 201 Synthesis of 3-[(E)-2-(4-methylsulfonylphenyl)ethenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manner as in Example 189, the free compound of the title compound was obtained (646 mg, yield; 70%) from 4-methylsulfonylvinylbenzene (638 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (700 mg). The resulting free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 170-174°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 3.17-3.25(m,2H), 3.25(s,3H), 3.32-3.39(m,2H), 3.50-3.57(m,2H), 3.63(d,J=11.6Hz,2H), 4.01(d,J=13.6Hz,2H), 7.59(d,J=15.6Hz,1H), 7.60(s,1H), 7.62(t,J=8.0Hz,1H), 7.75(t,J=8.0Hz,1H), 7.77(d,J=15.6Hz,1H), 7.94(br,4H), 7.95(d,J=8.0Hz,1H), 8.11(d,J=8.0Hz,1H).

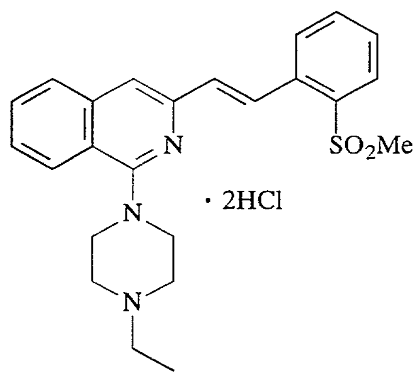
MS(FAB) m/z 422(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.19(t,J=7.2Hz,3H), 2.57(q,J=7.2Hz,2H), 2.77(br,4H), 3.08(s,3H), 3.58(br,4H),

7.25(s,1H), 7.30(d,J=15.6Hz,1H), 7.48(ddd,J=8.4,8.0,1.2Hz,1H), 7.59(ddd,J=8.4,8.0,1.2Hz,1H), 7.74(d,J=8.0Hz,1H), 7.75(d,J=8.4Hz,2H), 7.81(d,J=15.6Hz,1H), 7.93(d,J=8.4Hz,2H), 8.07(d,J=8.4Hz,1H).

Example 202 Synthesis of 3-[(E)-2-(2-methylsulfonylphenyl)ethenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manner as in Example 189, the free compound of the title compound was obtained (599 mg, yield; 84%) from 2-methylsulfonylvinylbenzene (500 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (549 mg). The resulting free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 146-149°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 3.18-3.25(m,2H), 3.30(s,3H), 3.33-3.45(m,2H), 3.58-3.67(m,4H), 4.02-4.07(m,2H), 7.50(d,J=15.6Hz,1H), 7.56(s,1H), 7.58(dd,J=8.0,1.2Hz,1H), 7.60(t,J=8.0Hz,1H),

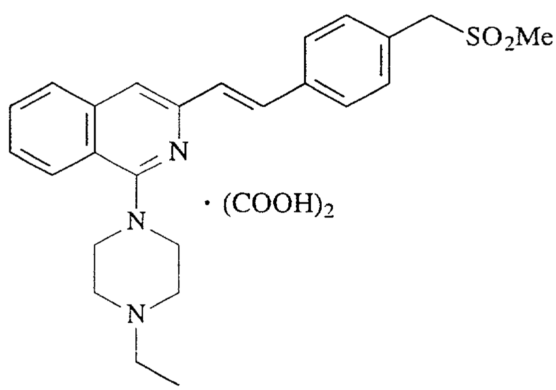
7.62(t,J=8.0Hz,1H), 7.75(t,J=8.0Hz,1H), 7.79(t,J=8.0Hz,1H), 7.95(d,J=8.0Hz,1H), 8.00(dd,J=8.0,1.2Hz,1H), 8.11(d,J=8.0Hz,1H), 8.66(d,J=15.6Hz,1H).

MS(FAB) m/z 422$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.56(br,4H), 3.15(s,3H), 3.63(br,4H), 7.19(d,J=15.6Hz,1H), 7.26(s,1H), 7.43-7.57(m,2H), 7.60(ddd,J=8.4,8.0,1.2Hz,1H), 7.64(ddd,J=8.4,8.0,1.2Hz,1H), 7.74(d,J=8.0Hz,1H), 7.87(d,J=7.2Hz,1H), 8.06(d,J=8.4Hz,1H), 8.12(d,J=8.0,1.2Hz,1H), 8.74(d,J=15.6Hz,1H).

Example 203 Synthesis of 3-[(E)-2-(4-methylsulfonylmethylphenyl)ethenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



In the same manner as in Example 189, the free compound of the title compound was obtained (496 mg, yield; 78%) from 4-methylsulfonylmethylstyrene (432 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (470 mg). The resulting free compound was converted into an oxalate in a conventional

manner, to give the oxalate of the title compound as yellow crystals.

Oxalate:

m.p.; 245-247°C

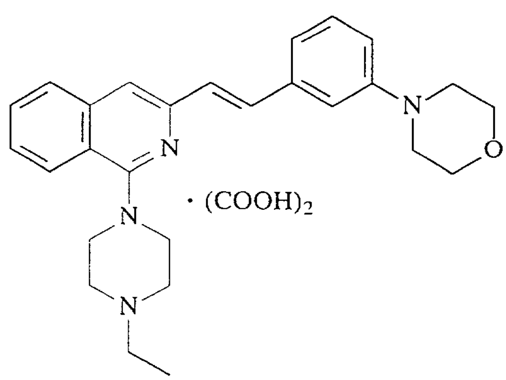
^{1}H-NMR(400MHz,DMSO-d_3); δ (ppm) 1.28(t,J=7.2Hz,3H), 2.93(s,3H), 3.18(q,J=7.2Hz,2H), 3.42(br,4H), 3.67(br,4H), 4.52(s,2H), 7.40(d,J=15.6Hz,1H), 7.44(d,J=8.4Hz,2H), 7.52(s,1H), 7.59(t,J=8.0Hz,1H), 7.70(d,J=8.4Hz,2H), 7.71(d,J=15.6Hz,1H), 7.72(t,J=8.0Hz,1H), 7.91(d,J=8.0Hz,1H), 8.10(d,J=8.0Hz,1H).

MS(FAB) m/z 436(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.19(t,J=7.2Hz,3H), 2.58(q,J=7.2Hz,2H), 2.78(br,7H), 3.58(br,4H), 4.27(s,2H), 7.20(d,J=15.6Hz,1H), 7.22(s,1H), 7.41(d,J=8.4Hz,2H), 7.45(ddd,J=8.4,8.0,1.2Hz,1H), 7.58(ddd,J=8.4,8.0,1.2Hz,1H), 7.63(d,J=8.4Hz,2H), 7.72(d,J=8.0Hz,1H), 7.78(d,J=15.6Hz,1H), 8.06(d,J=8.4Hz,1H).

Example 204 Synthesis of 3-{(E)-2-[3-(4-morpholinyl)phenyl]ethenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



In the same manner as in Example 189, the free compound of the title compound was obtained (600 mg, yield; 95%) from 3-(4-morpholinyl)styrene (417 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (470 mg). The resulting free compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as yellow crystals.

Oxalate:

m.p.; 180-182°C

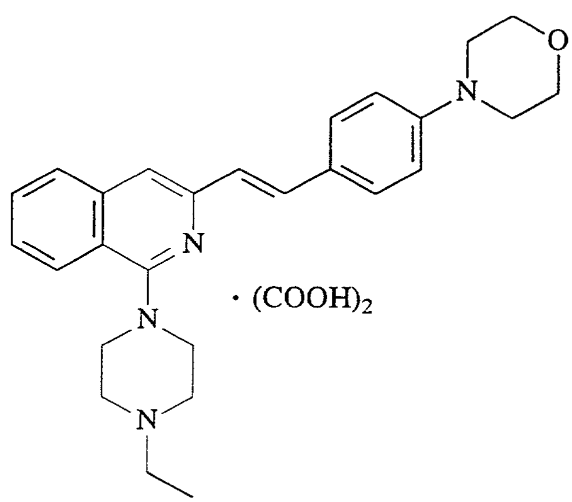
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.28(t,J=7.2Hz,3H), 3.18(br,6H), 3.43(br,4H), 3.66(br,4H), 3.77(t,J=4.8Hz,4H), 6.91(dd,J=8.0,2.0Hz,1H), 7.12(d,J=8.0Hz,1H), 7.21(br,1H), 7.26(t,J=8.0Hz,1H), 7.36(d,J=16.0Hz,1H), 7.49(s,1H), 7.58(t,J=8.0Hz,1H), 7.65(d,J=16.0Hz,1H), 7.72(t,J=8.0Hz,1H), 7.89(d,J=8.0Hz,1H), 8.09(d,J=8.0Hz,1H).

MS(FAB) m/z 429(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.76(br,4H), 3.22(t,J=4.8Hz,4H), 3.56(br,4H), 3.89(t,J=4.8Hz,4H), 6.84(dd,J=7.6,1.2Hz,1H), 7.12-7.17(m,2H), 7.15(d,J=16.0Hz,1H), 7.19(s,1H), 7.28(dt,J=7.6Hz,1H), 7.42(t,J=8.0Hz,2H), 7.55(t,J=8.0Hz,1H), 7.70(d,J=8.0Hz,1H), 7.74(d,J=16.0Hz,1H), 8.04(d,J=8.0Hz,1H).

Example 205 Synthesis of 3-{(E)-2-[4-(4-morpholinyl)phenyl]ethenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



In the same manner as in Example 189, the free compound of the title compound was obtained (157 mg, yield; 36%) from 4-(4-morpholinyl)styrene (284 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (320 mg). The resulting free compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as yellow crystals.

Oxalate:

m.p.; 248-250°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.29(t,J=7.2Hz,3H), 3.18(br,4H), 3.24(q,J=7.6Hz,2H), 3.48(br,6H), 3.75(br,6H), 6.98(d,J=8.8Hz,2H), 7.15(d,J=16.0Hz,1H), 7.43(s,1H), 7.53(d,J=8.8Hz,2H), 7.55(t,J=8.0Hz,1H), 7.61(d,J=16.0Hz,1H), 7.69(t,J=8.0Hz,1H), 7.86(d,J=8.0Hz,1H), 8.07(d,J=8.0Hz,1H).

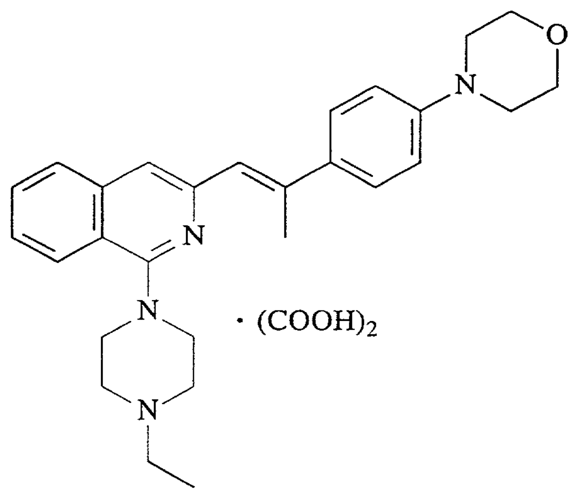
MS(FAB) m/z 429(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.6Hz,3H), 2.56(q,J=7.6Hz,2H), 2.56(br,4H), 3.21(t,J=4.8Hz,4H),

3.56(br,4H), 3.87(t,J=4.8Hz,4H), 6.90(d,J=8.8Hz,2H), 7.05(d,J=15.6Hz,1H), 7.15(s,1H), 7.40(ddd,J=8.4,8.0,1.2Hz,1H), 7.52(d,J=8.8Hz,2H), 7.54(ddd,J=8.4,8.0,1.2Hz,1H), 7.68(d,J=8.0Hz,1H), 7.73(d,J=15.6Hz,1H), 8.03(d,J=8.4Hz,1H).

Example 206 Synthesis of 3-{(E)-2-methyl-2-[4-(4-morpholinyl)phenyl]ethenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



In the same manner as in Example 189, the free compound of the title compound was obtained (475 mg, yield; 66%) from 4-(4-morpholinyl)-α-methylstyrene (500 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (523 mg). The resulting free compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as yellow crystals.

Oxalate:

m.p.; 266-267°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.27(t,J=7.2Hz,3H), 2.66(s,3H),

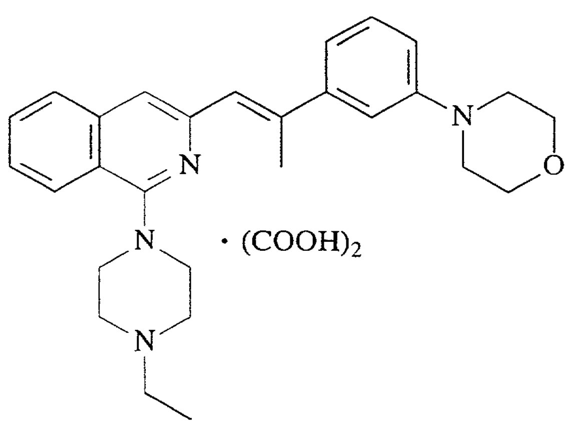
3.16(br,6H), 3.41(br,6H), 3.76(br,6H), 6.84(s,1H), 6.98(d,J=8.8Hz,2H), 7.50(s,1H), 7.51(d,J=8.8Hz,2H), 7.56(t,J=8.0Hz,1H), 7.70(t,J=8.0Hz,1H), 7.87(d,J=8.0Hz,1H), 8.08(d,J=8.0Hz,1H).

MS(FAB) m/z 443$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.73(s,3H), 2.76(br,4H), 3.21(t,J=4.8Hz,4H), 3.52(br,4H), 3.88(t,J=4.8Hz,4H), 6.79(s,1H), 6.92(d,J=8.8Hz,2H), 7.21(s,1H), 7.42(ddd,J=8.4,8.0,1.2Hz,1H), 7.52(d,J=8.8Hz,2H), 7.55(ddd,J=8.4,8.0,1.2Hz,1H), 7.70(t,J=8.0Hz,1H), 8.05(d,J=8.4Hz,1H).

Example 207 Synthesis of 3-{(E)-2-methyl-2-[3-(4-morpholinyl)phenyl]ethenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



In the same manner as in Example 189, the free compound of the title compound was obtained (332 mg, yield; 35%) from 3-(4-morpholinyl)-α-methylstyrene (658 mg) and 3-bromo-1-

(4-ethylpiperazin-1-yl)isoquinoline (691 mg). The resulting free compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as yellow crystals.

Oxalate:

m.p.; 190-192°C

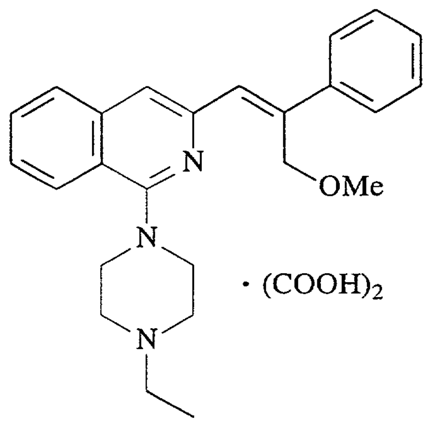
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.28(t,J=7.2Hz,3H), 2.67(s,3H), 3.17(t,J=4.8Hz,6H), 3.21(q,J=7.2Hz,2H), 3.47(br,6H), 3.77(t,J=4.8Hz,4H), 6.87(s,1H), 6.92(dd,J=8.0,2.0Hz,1H), 7.04(d,J=8.0Hz,1H), 7.11(br,1H), 7.26(t,J=8.0Hz,1H), 7.55(s,1H), 7.59(t,J=8.0Hz,1H), 7.72(t,J=8.0Hz,1H), 7.89(d,J=8.0Hz,1H), 8.10(d,J=8.0Hz,1H).

MS(FAB) m/z 443(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.74(s,3H), 2.75(br,4H), 3.22(t,J=4.8Hz,4H), 3.52(br,4H), 3.89(t,J=4.8Hz,4H), 6.79(s,1H), 6.86(dd,J=8.0,2.4Hz,1H), 7.09(d,J=8.0Hz,1H), 7.10(s,1H), 7.22(s,1H), 7.29(t,J=8.0Hz,1H), 7.44(t,J=7.6Hz,1H), 7.56(t,J=7.6Hz,1H), 7.70(d,J=7.6Hz,1H), 8.05(d,J=7.6Hz,1H).

Example 208 Synthesis of 3-[(E)-2-methoxymethyl-2-phenylethenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



In the same manner as in Example 189, the free compound of the title compound (492 mg, yield; 71%) from α-methoxymethylstyrene (403 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (580 mg). The resulting free compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as yellow crystals.

Oxalate:

m.p.; 180-182°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.23(t,J=7.2Hz,3H), 3.05(br,2H), 3.25(br,4H), 3.49(br,4H), 3.75(s,3H), 3.95(s,2H), 6.91(s,1H), 7.10(t,J=7.6Hz,1H), 7.15(s,1H), 7.23(t,J=7.6Hz,2H), 7.42(d,J=7.6Hz,2H), 7.50(t,J=8.0Hz,1H), 7.62(t,J=8.0Hz,1H), 7.76(d,J=8.0Hz,1H), 8.01(d,J=8.0Hz,1H).

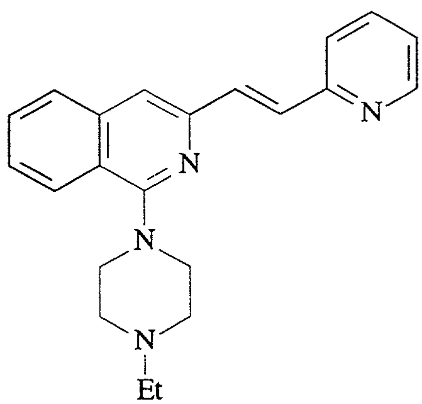
MS(FAB) m/z 388(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 2.53(q,J=7.2Hz,2H), 2.70(br,4H), 3.45(br,4H), 3.75(s,3H), 4.04(s,2H), 6.65(s,1H), 7.08(s,1H), 7.12(dt,J=7.6,1.2Hz,1H),

7.22(t,J=7.6Hz,2H), 7.36(ddd,J=8.4,8.0,1.2Hz,1H), 7.42(dd,J=7.6,1.2Hz,2H), 7.49(ddd,J=8.4,8.0,1.2Hz,1H), 7.59(d,J=8.0Hz,1H), 7.99(d,J=8.4Hz,1H).

Example 209 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[trans-2-(2-pyridyl)ethenyl]isoquinoline trihydrochloride



In the same manner as in Example 189, the hydrochloride of the title compound was obtained as yellow crystals (789 mg, yield; 77%) from 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (714 mg) and 2-vinylpyridine (469 mg).

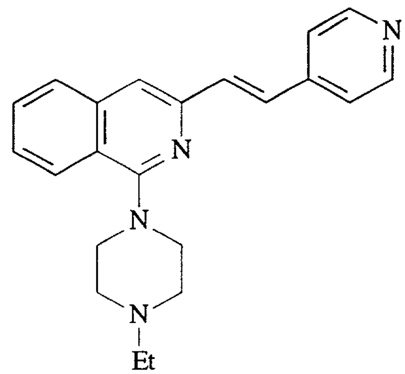
Hydrochloride:

m.p.; 220°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(3H,t,J=7.2Hz), 3.20(1H,q,J=7.2Hz), 3.22(1H,q,J=7.2Hz), 3.32(1H,t,J=11.2Hz), 3.35(1H,t,J=11.2Hz), 3.56(2H,t,J=13.6Hz), 3.58(2H,d,J=11.2Hz), 4.00(2H,d,J=13.6Hz), 7.58-7.67(3H,m), 7.73-7.77(1H,m), 7.88-8.01(2H,m), 7.95(1H,d,J=15.6Hz), 8.10-8.15(2H,m), 8.18-8.25(1H,m), 8.70(1H,d,J=4.4Hz), 11.06(1H,br-s).

ESI-Mass; 345(MH^+).

Example 210 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[trans-2-(4-pyridyl)ethenyl]isoquinoline



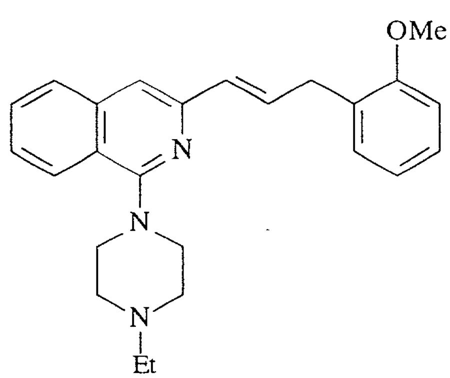
In the same manner as in Example 189, the oxalate of the title compound as a yellow amorphous (468 mg, yield; 79 %) from 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (435 mg) and 4-vinylpyridine (286 mg).

Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.26(3H,t,J=7.2Hz), 3.17(2H,q,J=7.2Hz), 3.36-3.46(1H,m), 3.58-3.76(1H,m), 7.56-7.63(7H,m), 7.73(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.92(1H,d,J=8Hz), 8.10(1H,d,J=8Hz), 8.56(2H,dd,J=6Hz,1.6Hz).

ESI-Mass; 345(MH^+).

Example 211 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[3-(2-methoxy)phenyl-2-propenyl]isoquinoline oxalate



2-Allylphenol (444 mg) was dissolved in N,N-dimethylformamide (5 ml), followed by the addition of 60% sodium hydride (157 mg). The resulting mixture was stirred at room temperature for 20 min. Methyl iodide (250 ml) was added thereto, and the mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (563 mg) were treated in the same manner as in Example 189, to give the oxalate of the title compound as a pale red amorphous (400 mg, yield; 44%).

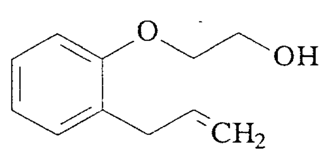
Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.21(3H,t,J=7.2Hz), 3.05(2H,q,J=7.2Hz), 3.20-3.36(4H,m), 3.52(2H,d,J=2.4Hz), 3.80(3H,s), 6.47(1H,d,J=15.2Hz), 6.87-6.94(2H,m), 6.99(1H,d,J=8.4Hz), 7.16-7.24(2H,m), 7.27(1H,s), 7.51(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.65(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.81(1H,d,J=8Hz), 8.02(1H,d,J=8Hz).

FAB-Mass; 388(MH^+).

Example 212 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[3-(2-hydroxyethoxy)phenyl-1-propenyl]isoquinoline oxalate

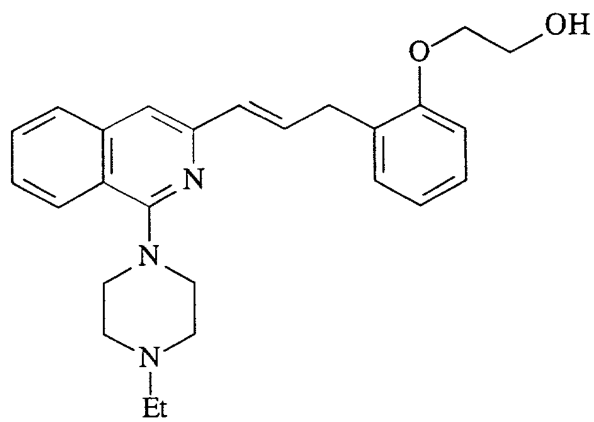
(212-1) 2-(2-Allylphenoxy)ethanol



2-Allylphenol (5.066 g) was dissolved in N,N-dimethylformamide (70 ml), followed by the addition of methyl 2-bromoacetate (6.931 g) and potassium carbonate (7.88 g), and the resulting mixture was stirred at 100°C overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was dissolved in tetrahydrofuran (40 ml), followed by the addition of lithium aluminium hydride (1.442 g) in small portions under ice-cooling. The resulting mixture was stirred for 5 min. To the reaction mixture were sequentially added water (1.5 ml), 5N sodium hydroxide (1.5 ml) and water (4.5 ml), and the resulting insoluble matters were filtered off through Celite. The resulting filtrate was partitioned between ethyl acetate and water. The organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by (NH) silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a colorless oil (5.248 mg, yield; 76%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 3.41(2H,d,J=6.4Hz), 3.93-3.98(2H,m), 4.09(2H,t,J=4.4Hz), 5.00-5.07(2H,m), 5.94-6.05(1H,m), 6.85(1H,dd,J=7.6Hz,1.6Hz), 6.93(1H,td,J=7.6Hz,1.6Hz), 7.16(1H,dd,J=7.6Hz,1.6Hz), 7.20(1H,td,J=7.6Hz,1.6Hz).

<u>(212-2) 1-(1-Ethylpiperazin-4-yl)-3-[3-(2-hydroxyethoxy)phenyl-1-propenyl]isoquinoline oxalate</u>



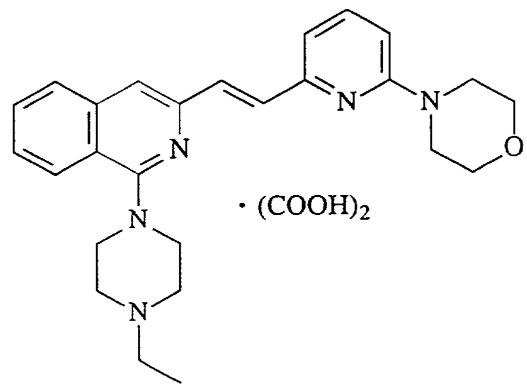
In the same manner as in Example 189, the oxalate of the title compound was obtained as a pale yellow amorphous (313 mg, yield; 38%) from 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (528 mg) and 2-(2-allylphenoxy)ethanol (570 mg).

Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.20(3H,t,J=7.2Hz), 3.02(2H,q,J=7.2Hz), 3.16-3.30(4H,m), 3.42-3.60(4H,m), 3.55(2H,d,J=7.2Hz), 3.75(2H,t,J=5Hz), 4.01(2H,t,J=5Hz), 6.53(1H,d,J=15.2Hz), 6.88(1H,td,J=7.6Hz,1Hz), 6.94(1H,dt,15.2Hz,7.2Hz), 6.97(1H,dd,J=8.2Hz,1Hz), 7.18(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.65(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.81(1H,d,J=8Hz), 8.02(1H,d,J=8Hz).

ESI-Mass; 418(MH^+).

Example 213 Synthesis of 3-{(E)-2-[2-(4-morpholinyl)pyridin-5-yl]ethenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



In the same manner as in Example 189, the free compound of the title compound was obtained (750 mg, yield; 94%) from 2-(4-morpholinyl)-5-vinylpyridine (708 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (595 mg). The resulting free compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as yellow crystals.

Oxalate:

m.p.; 124-128°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.28(t,J=7.2Hz,3H), 3.19(br,2H), 3.43(br,4H), 3.54(t,J=4.8Hz,6H), 3.75(t,J=4.8Hz,6H), 6.79(d,J=8.4Hz,1H), 6.89(d,J=7.2Hz,1H), 7.56(d,J=15.2Hz,1H), 7.57-7.64(m,3H), 7.65(d,J=15.2Hz,1H), 7.73(t,J=8.0Hz,1H), 7.90(d,J=8.0Hz,1H), 8.10(d,J=8.0Hz,1H).

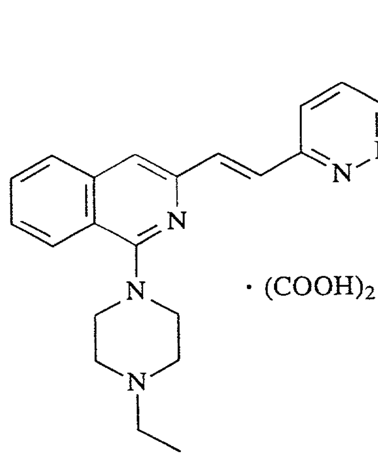
MS(FAB) m/z 430(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.76(br,4H), 3.57(br,4H), 3.62(t,J=4.8Hz,4H), 3.88(t,J=4.8Hz,4H), 6.54(d,J=8.4Hz,1H), 6.81(d,J=6.8Hz,1H), 7.27(s,1H), 7.44(ddd,J=8.4,8.0,1.2Hz,1H),

7.50(dd,J=8.4,6.8Hz,1H), 7.55(ddd,J=8.4,8.0,1.2Hz,1H), 7.67(br,1H), 7.71(d,J=8.0Hz,1H), 8.05(d,J=8.4Hz,1H).

Example 214 Synthesis of 3-{(E)-2-[3-(4-morpholinyl)pyridazin-6-yl]ethenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



In the same manner as in Example 189, the free compound of the title compound was obtained (560 mg, yield; 87%) from 3-(4-morpholinyl)-6-vinylpyridazine (567 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (476 mg). The resulting free compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as yellow crystals.

Oxalate:

m.p.; 88-90°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.30(t,J=7.2Hz,3H), 3.28(q,J=7.2Hz,2H), 3.40(br,2H), 3.62(t,J=4.8Hz,6H), 3.75(t,J=4.8Hz,6H), 4.02(br,2H), 7.36(d,J=9.6Hz,1H), 7.55(s,1H), 7.56(d,J=16.0Hz,1H), 7.62(t,J=8.0Hz,1H), 7.74(t,J=8.0Hz,1H), 7.82(d,J=16.0Hz,1H), 7.93(d,J=9.6Hz,1H),

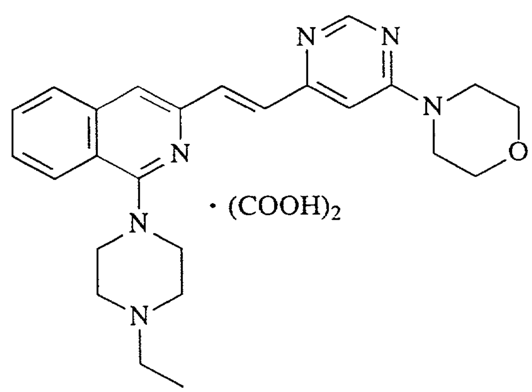
7.94(d,J=8.0Hz,1H), 8.12(d,J=8.0Hz,1H).

MS(FAB) m/z 431$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.75(br,4H), 3.58(br,4H), 3.67(t,J=4.8Hz,4H), 3.86(t,J=4.8Hz,4H), 6.89(d,J=9.6Hz,1H), 7.23(s,1H), 7.45(t,J=8.0Hz,1H), 7.49(d,J=15.6Hz,1H), 7.51(d,J=9.6Hz,1H), 7.57(d,J=8.0Hz,1H), 7.72(d,J=8.0Hz,1H), 7.91(d,J=15.6Hz,1H), 8.05(d,J=8.0Hz,1H).

Example 215 Synthesis of 3-{(E)-2-[4-(4-morpholinyl)pyrimidin-6-yl]ethenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



In the same manner as in Example 189, the free compound of the title compound was obtained (380 mg, yield; 70%) from 4-(4-morpholinyl)-6-vinylpyrimidine (360 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (400 mg). The resulting free compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as yellow crystals.

Oxalate:

m.p.; 130-134°C

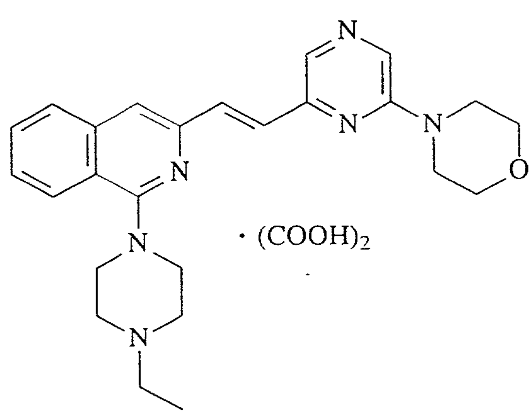
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.31(t,J=7.2Hz,3H), 3.29(q,J=7.2Hz,2H), 3.39(br,2H), 3.63(br,2H), 3.74(br,10H), 4.03(br,2H), 7.19(s,1H), 7.56(d,J=16.0Hz,1H), 7.64(s,1H), 7.66(t,J=8.0Hz,1H), 7.78(t,J=8.0Hz,1H), 7.93(d,J=16.0Hz,1H), 7.98(d,J=8.0Hz,1H), 8.14(d,J=8.0Hz,1H), 8.62(s,1H).

MS(FAB) m/z 431$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.76(br,4H), 3.58(br,4H), 3.69(t,J=4.8Hz,4H), 3.82(t,J=4.8Hz,4H), 6.60(s,1H), 7.29(s,1H), 7.48(ddd,J=8.4,8.0,1.2Hz,1H), 7.60(d,J=14.8Hz,1H), 7.59(ddd,J=8.4,8.0,1.2Hz,1H), 7.74(d,J=8.0Hz,1H), 7.84(d,J=14.8Hz,1H), 8.06(d,J=8.4Hz,1H), 8.64(s,1H).

Example 216 Synthesis of 3-{(E)-2-[2-(4-morpholinyl)pyrazin-6-yl]ethenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



In the same manner as in Example 189, the free compound of the title compound was obtained (295 mg, yield; 69%) from 2-(4-morpholinyl)-6-vinylpyrazine (287 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (320 mg). The resulting free compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as yellow crystals.

Oxalate:

m.p.; 173-175°C

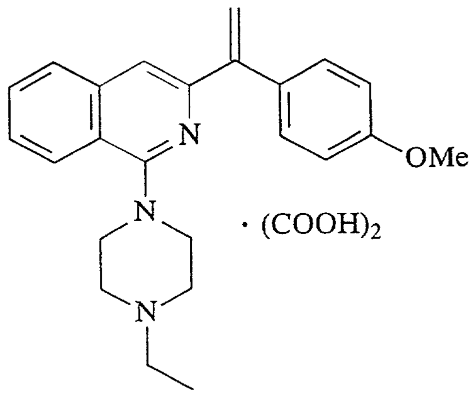
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.29(t,J=7.2Hz,3H), 3.25(q,J=7.2Hz,2H), 3.49(br,4H), 3.64(br,6H), 3.77(br,6H), 7.60(d,J=15.2Hz,1H), 7.62(t,J=8.0Hz,1H), 7.65(s,1H), 7.75(t,J=8.0Hz,1H), 7.75(d,J=15.2Hz,1H), 7.93(d,J=8.0Hz,1H), 8.08(s,1H), 8.12(d,J=8.0Hz,1H), 8.25(s,1H).

MS(FAB) m/z 431(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.77(br,4H), 3.58(br,4H), 3.66(t,J=4.8Hz,4H), 3.89(t,J=4.8Hz,4H), 7.29(s,1H), 7.47(dt,J=8.0,1.2Hz,2H), 7.58(dt,J=8.0,1.2Hz,1H), 7.69(s,1H), 7.70(s,1H), 7.72(d,J=8.0Hz,1H), 8.01(s,1H), 8.02(s,1H), 8.06(d,J=8.0Hz,1H).

Example 217 Synthesis of 3-[1-(4-methoxyphenyl)ethenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



A 5N aqueous solution of hydrochloric acid (2 ml) was added to 3-[α-methyl-α-hydroxy-(4-methoxybenzyl)]-1-(4-ethylpiperazin-1-yl)isoquinoline (600 mg)/ethanol (10 ml) solution, and the resulting mixture was reacted with heating under reflux for 1 hr. The reaction solution was evaporated, and then basified with a 1N aqueous solution of sodium hydroxide and extracted with ethyl acetate. The resulting organic layer was washed with brine, dried and evaporated. The resulting residue was purified by NH-silica gel column chromatography (ethyl acetate/hexane system), to give a yellow oil (352 mg, yield; 62%). The resulting oil was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 106-108°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.23(t,J=7.2Hz,3H), 3.05(br,2H), 3.27(br,4H), 3.60(br,4H), 3.80(s,3H), 5.46(s,1H), 6.14(s,1H), 6.98(d,J=8.8Hz,2H), 7.27(s,1H), 7.34(d,J=8.8Hz,2H), 7.60(t,J=8.0Hz,1H), 7.68(d,J=8.0Hz,1H),

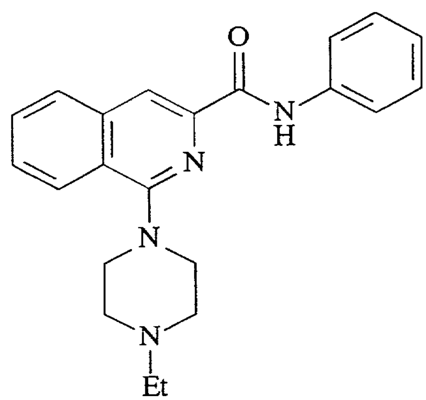
7.86(d,J=8.0Hz,1H), 8.10(d,J=8.0Hz,1H).

MS(FAB) m/z 362$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.74(br,4H), 3.54(br,4H), 3.86(s,3H), 5.44(d,J=2.4Hz,1H), 6.33(d,J=2.4Hz,1H), 6.93(d,J=8.8Hz,2H), 7.09(s,1H), 7.38(d,J=8.8Hz,2H), 7.44(ddd,J=8.4,8.0,1.2Hz,1H), 7.52(ddd,J=8.4,8.0,1.2Hz,1H), 7.61(d,J=8.0Hz,1H), 8.06(d,J=8.0Hz,1H).

<u>Example 218</u> <u>Synthesis of 1-(1-ethylpiperazin-4-yl)-N-phenyl-3-isoquinolinecarboxamide dihydrochloride</u>



Isocarbostyryl-3-carboxylic acid (366 mg) synthesized according to Nippon Kagaku Zasshi (the Japanese Chemical Journal), <u>81</u> (6), 106, 1960 was added to phosphorus oxychloride (4 ml), which was then stirred at 110°C for 20 min. The reaction solution was evaporated, and the resulting residue was dissolved in toluene (5 ml). A solution mixture of aniline (2 ml)/toluene (3 ml) was added thereto, and the mixture was stirred for 15 min. The reaction mixture was partitioned

between ethyl acetate and 1N hydrochloric acid. The organic layer was washed with water, dried (over $MgSO_4$) and evaporated. 1-Ethylpiperadine (5 ml) was added to the resulting residue, which was then stirred at 120°C for 30 min. The reaction solution was evaporated, and then partitioned between ethyl acetate and water. The organic layer was washed with water, dried (over $MgSO_4$) and evaporated, and the resulting residue was purified by silica gel column chromatography (ethyl acetate/acetone system). The resulting product was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title (504 mg, yield; 63%) as colorless crystals.

Hydrochloride:

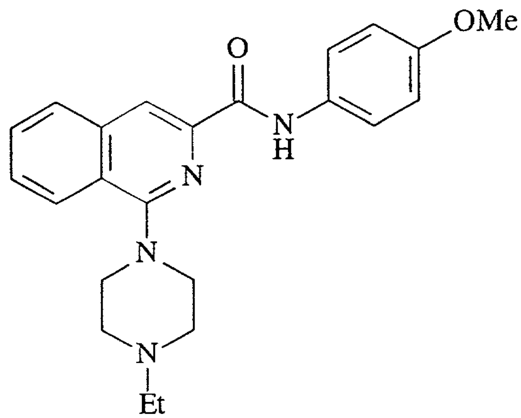
m.p.; 260°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.32(3H,t,J=7.2Hz), 3.21(1H,q,J=7.2Hz), 3.23(1H,q,J=7.2Hz), 3.33(1H,t,J=11.6Hz), 3.36(1H,t,J=11.6Hz), 3.54-3.62(4H,m), 4.18(2H,d,J=14Hz), 7.14(1H,tt,J=7.6Hz,0.8Hz), 7.40(2H,dd,J=7.6Hz,7.6Hz), 7.75(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.82(2H,dd,J=7.6Hz,0.8Hz), 7.83(1H,ddd,J=8Hz,7Hz,1.2Hz), 8.17(1H,d,J=8Hz), 8.19(1H,d,J=8Hz), 8.27(1H,s), 10.20(1H,s), 11.00(1H,br-s).

ESI-Mass; 361(MH^+).

<u>Example 219</u> <u>Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(4-methoxyanilinomethyl)isoquinoline oxalate</u>

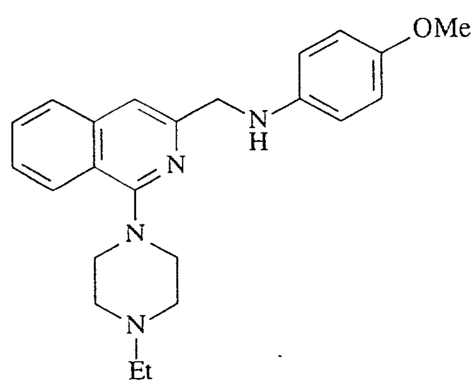
<u>(219-1)</u> <u>1-(1-Ethylpiperazin-4-yl)-3-N-(4-methoxyphenyl)isoquinolinecarboxamide</u>



In the same manner as in Example 218, 793 mg of the title compound was obtained as a brown oil from isocarbostyryl-3-carboxylic acid (741 mg) and p-anisidine (961 mg).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.19(3H,t,J=7.2Hz), 2.57(2H,q,J=7.2Hz), 2.78(4H,t,J=4.4Hz), 3.54(4H,t,J=4.4Hz), 3.82(3H,s), 6.94(2H,d,J=8.8Hz), 7.60(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.67(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.70(2H,d,J=8.8Hz), 7.91(1H,dd,J=8Hz,1.2Hz), 8.14(1H,dd,J=8Hz,1.2Hz), 8.27(1H,s), 10.03(1H,s).

(219-2) 1-(1-Ethylpiperazin-4-yl)-3-(4-methoxyanilinomethyl)isoquinoline oxalate



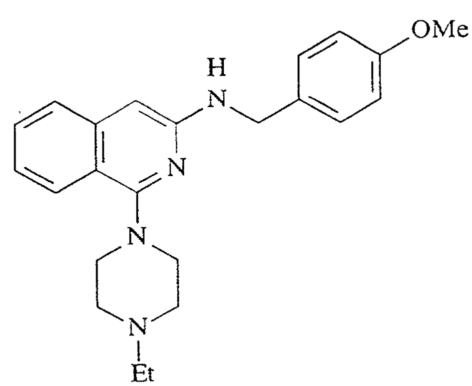
1-(1-Ethylpiperazin-4-yl)-3-N-(4-methoxyphenyl)isoquinolinecarboxamide (793 mg) was dissolved

in tetrahydrofuran (15 ml), followed by the addition of lithium aluminum hydride (456 mg), and the mixture was stirred at 40°C overnight. Water (0.5 ml), 1N sodium hydroxide (0.5 ml) and water (1.5 ml) were sequentially added thereto, and the resulting insoluble matters were filtered off through Celite. The resulting filtrate was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by (NH) silica gel column chromatography (ethyl acetate/hexane system). The resulting product was converted into an oxalate in a conventional manner, to give the title compound as a dark yellow amorphous (43 mg, yield; 5%).

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.24(3H,t,J=7.2Hz), 3.12(2H,q,J=7.2Hz), 3.25-3.42(4H,m), 3.59(2H,s), 3.46-3.84(4H,m), 3.78(3H,s), 6.55(1H,d,J=9.2Hz), 6.67(1H,d,J=9.2Hz), 6.94-7.02(2H,m), 7.37(1H,d,J=9.2Hz), 7.64-7.84(2H,m), 8.04-8.20(2H,m).

ESI-Mass; 377(MH^+).

Example 220 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(4-methoxybenzylamino)isoquinoline oxalate



In the same manner as in Example 158, the oxalate of the title compound was obtained as a pale yellow amorphous (164 mg, yield; 42%) from 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (760 mg) and 4-methoxybenzylamine (449 mg).

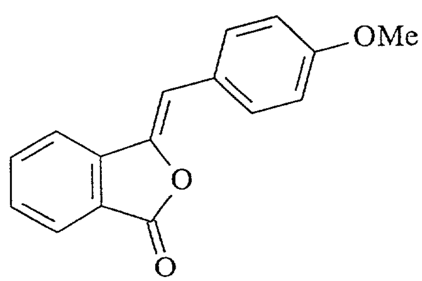
Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.16(3H,t,J=7.2Hz), 2.52(1H,t,J=4.8Hz), 2.88(2H,q,J=7.2Hz), 3.00-3.12(4H,m), 3.38-3.46(4H,m), 3.69(3H,s), 4.36(2H,d,J=4.8Hz), 6.18(1H,s), 6.85(2H,d,J=8.8Hz), 7.05(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.27(2H,d,J=8.8Hz), 7.35(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.40(1H,d,J=8Hz), 7.76(1H,d,J=8Hz).

FAB-Mass; 377(MH^+).

Example 221 Synthesis of 1-(1-ethylpiperazin-4-yl)-4-methoxy-3-(4-methoxyphenyl)isoquinoline dihydrochloride

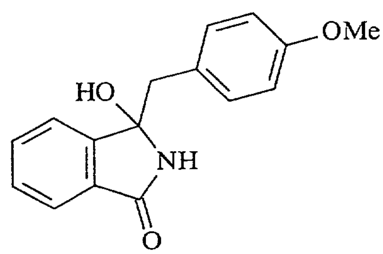
(221-1) 3-(4-Methoxybenzylidine)phthalide



A mixture of phthalic anhydride (100 g), 4-methoxyphenylacetic acid (110.897 g) and sodium acetate (2.6 g) was melted at 200-220°C for 6 hr. After the mixture was cooled to 90-95°C as it stands, ethanol (600 ml) was added thereto and the insoluble matters were collected by filtration, to give the title compound as a yellow solid (83.016 g, yield; 49%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 3.86(3H,s), 6.40(1H,s), 6.95(2H,d,J=8.8Hz), 7.52(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.71(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.75(1H,dt,J=8Hz,1.2Hz), 7.82(2H,d,J=8.8Hz), 7.94(1H,dt,J=8Hz,1.2Hz).

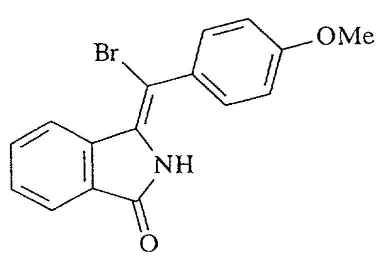
(221-2) 3-Hydroxy-3-(4-methoxybenzyl)phthalimidine



3-(4-Methoxybenzylidene)phthalide (15.168 g) was dissolved in ethanol (35 ml), followed by the addition of a 29% aqueous solution of ammonia (35 ml). The resulting mixture was stirred at 80°C for 1 hr. The reaction solution was evaporated, followed by the addition of ether and the resulting precipitates were collected by filtration, to give the title compound as a yellow solid (16.202 g, yield; 100%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 3.05(1H,d,J=13.8Hz), 3.33(1H,d,J=13.8Hz), 3.76(3H,s), 6.58(1H,br-s), 6.78(2H,d,J=8.8Hz), 7.211(2H,d,J=8.8Hz), 7.41(1H,t,J=7.6Hz), 7.48(1H,d,J=7.6Hz), 7.53-7.59(2H,m).

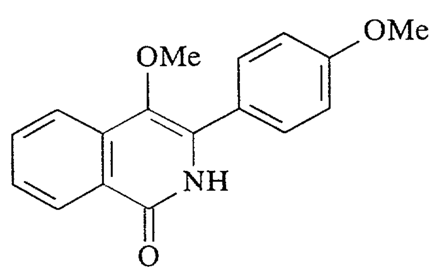
(221-3) (E)-3-(α-Bromo-4-methoxybenzylidene)phthalimidine



3-Hydroxy-3-(4-methoxybenzyl)phthalimidine (16.192 g) was dissolved in benzene (400 ml), N-bromosuccinimide (14.523 g) was added thereto and the resulting mixture was heated under reflux for 2 hr. The reaction mixture was cooled, the resulting precipitates were filtered off. Then, the filtrate was washed with water, dried (over $MgSO_4$), evaporated, and the resulting residue was recrystallized from ethanol/hexane, to give the title compound as pale yellow crystals (11.074 g, yield; 57%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 3.90(3H,s), 6.74(1H,dt,J=7.6Hz,0.8Hz), 7.00(2H,d,J=8.8Hz), 7.30(1H,td,J=7.6Hz,0.8Hz), 7.42(1H,td,J=7.6Hz,0.8Hz), 7.43(2H,d,J=8.8Hz), 7.83(1H,dt,J=7.6Hz,0.8Hz), 7.88(1H,br-s).

(221-4) 4-Methoxy-3-(4-methoxyphenyl)isoquinolin-1-(2H)-one

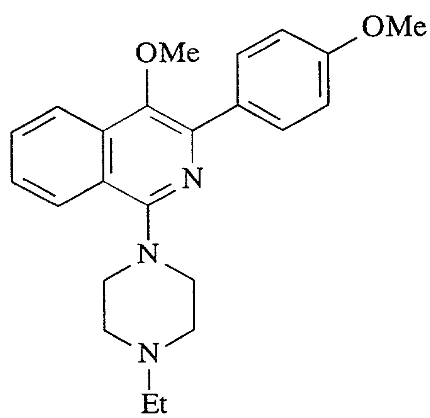


(E)-3-(α-Bromo-α-4-methoxybenzylidene)phthalimidine (4.031 g) and potassium hydroxide (1.6 g) were added to methanol (20 ml), and the resulting mixture was heated at 200-220°C for 1 hr. After cooling as it was, the reaction solution was evaporated, and the resulting residue was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. Ether was added

thereto, and the resulting insoluble matters were collected by filtration, to give the title compound as a pale yellow solid (1.786 g, yield; 52%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 3.54(3H,s), 3.89(3H,s), 7.04(2H,d,8.8Hz), 7.53(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.69(1H,dd,J=8Hz,1.2Hz), 7.76(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.89(1H,dd,J=8Hz,1.2Hz), 8.41(1H,dd,J=8Hz,1.2Hz), 8.50(1H,br-s).

(221-5) 1-(1-Ethylpiperazin-4-yl)-4-methoxy-3-(4-methoxyphenyl)isoquinoline dihydrochloride



4-Methoxy-3-(4-methoxyphenyl)isoquinolin-1-(2H)-one (1.263 g) was treated in the same manner as in Example 252-4, to give the hydrochloride of the title compound as colorless crystals (recrystallized from ethanol/isopropyl ether) (632 mg, yield; 31%).

Hydrochloride:

m.p.; 227-235°C

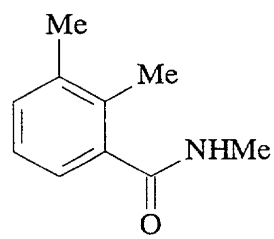
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.30(3H,t,J=7.2Hz), 3.20(1H,q,J=7.2Hz), 3.22(1H,q,J=7.2Hz), 3.26-3.38(2H,m),

3.44(2H,t,J=13.2Hz), 3.59(2H,d,J=11.2Hz), 3.63(3H,s), 3.82(3H,s), 3.85(2H,d,J=13.2Hz), 7.06(2H,d,J=8.8Hz), 7.67(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.80(1H,ddd,J=8Hz,7Hz,1.2Hz), 8.11(1H,d,J=8Hz), 8.12(1H,d,J=8Hz), 8.13(2H,d,J=8.8Hz), 10.80-10.90(1H,br-s).

ESI-Mass; 378(MH^+).

Example 222 Synthesis of 1-(1-ethylpiperazin-4-yl)-5-methyl-3-(4-methoxyphenyl)isoquinoline dihydrochloride

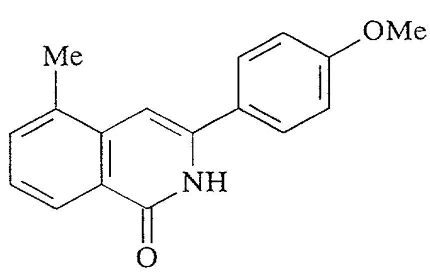
(221-1) 2,3-Dimethyl-N-methylbenzamide



In the same manner as in Example 225-1, the title compound was obtained as a colorless solid (10.99 g, yield; 100%) from 2,3-dimethylbenzoic acid (10.068 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 2.28(3H,s), 2.30(3H,s), 2.99(3H,d,J=4.8Hz), 5.76(1H,br-s), 7.09(1H,t,J=7.4Hz), 7.15(1H,d,J=7.4Hz), 7.18(1H,d,J=7.4Hz).

(222-2) 5-Methyl-3-(4-methoxyphenyl)isoquinolin-1-(2H)-one

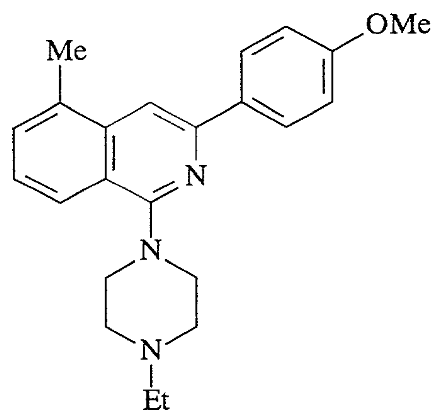


In the same manner as in Example 10-1, the title compound

was obtained as a pale yellow solid (3.456 g, yield; 42%) from 2,5-dimethyl-N-methylbenzamide (5.008 g) and anisonitrile (4.128 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 2.59(3H,s), 3.89(3H,s), 6.80(1H,s), 7.05(2H,d,J=8.8Hz), 7.36(1H,t,J=7.6Hz), 7.50(1H,d,J=7.6Hz), 7.67(2H,d,J=8.8Hz), 8.28(1H,d,J=7.6Hz), 9.75(1H,s).

(222-3) 1-(1-Ethylpiperazin-4-yl)-5-methyl-3-(4-methoxyphenyl)isoquinoline dihydrochloride



In the same manner as in Example 252-3, 5-methyl-3-(4-methoxyphenyl)isoquinolin-1-(2H)-one (1.003 mg) was treated, to give the hydrochloride of the title compound as yellow crystals (recrystallized in ethanol/isopropyl ether) (721 mg, yield; 45%).

Hydrochloride:

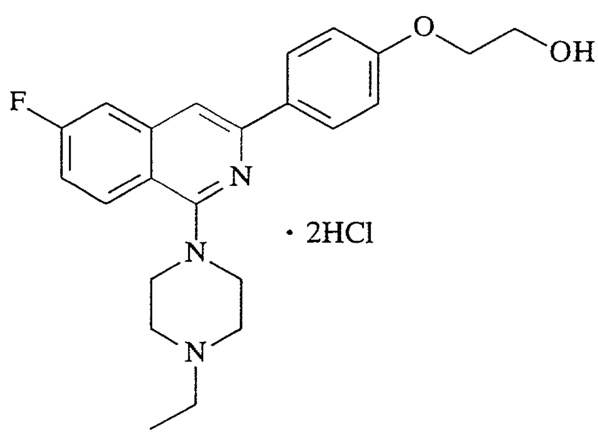
m.p.; 249-253°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.31(3H,t,J=7.2Hz), 2.68(3H,s), 3.18(1H,q,J=7.2Hz), 3.20(1H,q,J=7.2Hz), 3.30(1H,t,J=10.6Hz), 3.33(1H,t,J=10.6Hz), 3.49(2H,t,J=13.2Hz),

3.59(2H,d,J=10.6Hz), 3.81(3H,s), 3.92(2H,d,J=13.2Hz), 7.05(2H,d,J=8.8Hz), 7.43(1H,t,J=7.6Hz), 7.54(1H,d,J=7.6Hz), 7.92(1H,d,J=7.6Hz), 7.93(1H,s), 8.18(2H,d,J=8.8Hz), 10.06(1H,br-s).

ESI-Mass; 362(MH^+).

Example 223 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxyethoxy)phenyl]-6-fluoroisoquinoline dihydrochloride



From starting materials 4-(2-benzyloxyethoxy)-1-ethynylbenzene (7.64 g) and 2-bromo-4-fluorobenzalhyde (4.38 g), 3-[4-(2-benzyloxyethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)-6-fluoroisoquinoline was obtained according to Example 231. The resulting compound was hydrogenated in methanol in the presence of 10 % palladium -carbon, for debenzylation. The catalyst was filtered off, the resulting solution was washed with methanol, and then 0.90 g of the title compound was obtained directly as a hydrochloride.

Hydrochloride:

m.p.; 152-170°C

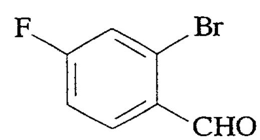
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.31(t,J=7.2Hz,3H), 3.14-

3.24(m,2H), 3.25-3.36(m,2H), 3.47-3.62(m,4H), 3.70-3.76(m,2H), 3.88-3.97(m,2H), 4.01-4.07(m,2H), 7.06(d,J=9.0Hz,2H), 7.38-7.45(m,1H), 7.66-7.72(m,1H), 7.96(s,1H), 8.10(d,J=9.0Hz,2H), 8.13-8.18(m,1H), 11.16-11.27(br,1H).

MS(FAB) m/z 396.00$(M+H)^+$.

Example 224 Synthesis of 1-(1-ethylpiperazin-4-yl)-6-fluoro-3-(4-methoxyphenyl)isoquinoline dihydrochloride

(224-1) 2-Bromo-4-fluorobenzaldehyde

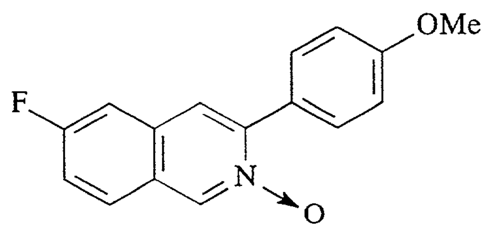


2-Bromo-4-fluorotoluene (10.215 g) was dissolved in ethyl acetate (100 ml), N-bromosuccinimide (11.3 g) and 70% benzoyl peroxide (200 mg) were added thereto, and the resulting mixture was stirred under heating at 80°C for 1 hr. After the reaction solution was cooled, the resulting insoluble matters were filtered off. The resulting filtrate was washed with an aqueous solution of saturated sodium bicarbonate, dried (over $MgSO_4$) and evaporated. The resulting residue was dissolved in acetic acid (30 ml), water (30 ml) and hexamethylene tetramine (15.141 g) were added thereto, and the resulting mixture was heated under stirring at 100°C for 1 hr. To the mixture was added 38% hydrochloric acid (20 ml), which was then stirred for 1 hr, and then it was cooled as it was, and extracted with ethyl acetate. The resulting organic phase was washed with an aqueous

solution of saturated sodium bicarbonate, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a colorless solid (4.376 g, yield; 41%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 7.14-7.19(1H,m), 7.40(1H,dd,J=8.4Hz,2.4Hz), 7.97(1H,dd,J=8.4Hz,6Hz), 10.30(1H,s).

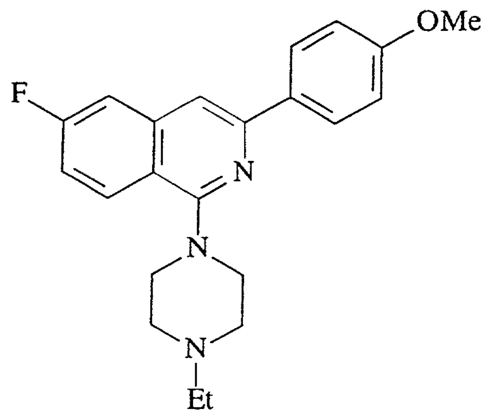
(224-2) 6-Fluoro-3-(4-methoxyphenyl)isoquinoline-2-oxide



2-Bromo-4-fluorobenzaldehyde (1.003 g) and 4-methoxyphenylacetylene (714 mg) were treated in the same manners as in Examples 177, 251-3 and 251-4 in this order, to give the title compound as a dark green solid (467 mg, yield; 35%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 3.88(3H,s), 7.03(2H,d,J=8.8Hz), 7.33-7.43(2H,m), 7.71-7.75(2H,m), 7.80(2H,d,J=8.8Hz), 8.89(1H,s).

(224-3) 1-(1-Ethylpiperazin-4-yl)-6-fluoro-3-(4-methoxyphenyl)isoquinoline dihydrochloride



In the same manner as in Example 251, the hydrochloride of the title compound was obtained as yellow crystals (187 mg, yield; 24%) from 6-fluoro-3-(4-methoxyphenyl)isoquinolin-2-oxide (467 mg).

Hydrochloride:

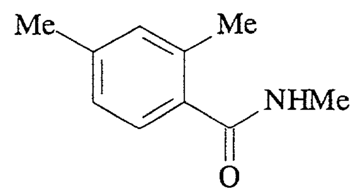
m.p.; 131-135°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.30(3H,t,J=7.2Hz), 3.20(1H,q,J=7.2Hz), 3.22(1H,q,J=7.2Hz), 3.30(1H,t,J=12Hz), 3.33(1H,t,J=12Hz), 3.49(2H,t,J=14Hz), 3.60(2H,d,J=12Hz), 3.81(3H,s), 3.95(2H,d,J=14Hz), 7.06(2H,d,J=8.8Hz), 7.42(1H,td,J=9.2Hz,2.8Hz), 7.70(1H,dd,J=9.8Hz,2.8Hz), 7.97(1H,s), 8.11(2H,d,J=8.8Hz), 8.16(1H,dd,J=9.2Hz,5.6Hz), 10.77(1H,br-s).

ESI-Mass; 366(MH^+).

<u>Example 225 Synthesis of 1-(1-ethylpiperazin-4-yl)-6-methyl-3-(4-methoxyphenyl)isoquinoline dihydrochloride</u>

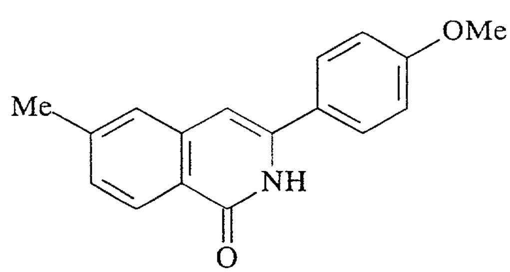
<u>(225-1) 2,4-Dimethyl-N-methylbenzamide</u>



2,4-Dimethylbenzoic acid (11.877 g) was added to thionyl chloride (30 ml), and the resulting mixture was stirred under heating for 45 min. The reaction solution was evaporated, and then dissolved in tetrahydrofuran (50 ml). To the mixture was added dropwise 40% methylamine/methanol solution (100 ml) under ice-cooling, and then it was stirred for 20 min. The resulting reaction solution was evaporated, and then partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated, to give the title compound as a colorless solid (12.281 g, yield; 95%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 2.32(3H,s), 2.42(3H,s), 2.99(3H,d,J=5.6Hz), 5.74(1H,br-s), 6.99(1H,d,J=8.4Hz), 7.03(1H,s), 7.25(1H,d,J=8.4Hz).

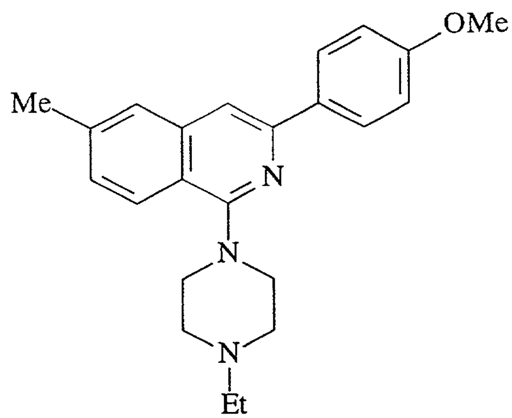
<u>(225-2) 6-Methyl-3-(4-methoxyphenyl)isoquinolin-1-(2H)-one</u>



In the same manner as in Example 10-1, the title compound was obtained as a pale yellow solid (3.140 g, yield; 39%) from 2,4-dimethyl-N-methylbenzamide (5.008 g) and anisonitrile (4.128 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 2.49(3H,s), 3.88(3H,s), 6.64(1H,s), 7.02(2H,d,J=8.8Hz), 7.27(1H,d,J=8Hz), 7.35(1H,s), 7.65(2H,d,J=8.8Hz), 8.27(1H,d,J=8Hz), 9.84(1H,br-s).

<u>(225-3)</u> <u>1-(1-Ethylpiperazin-4-yl)-6-methyl-3-(4-methoxyphenyl)isoquinoline dihydrochloride</u>



6-Methyl-3-(4-methoxyphenyl)isoquinolin-1-(2H)-one (1.024 mg) was treated in the same manner as in Example 252-3, to give the hydrochloride of the title compound as yellow crystals (recrystallized in ethanol/isopropyl ether) (1.084 g, yield; 64%).

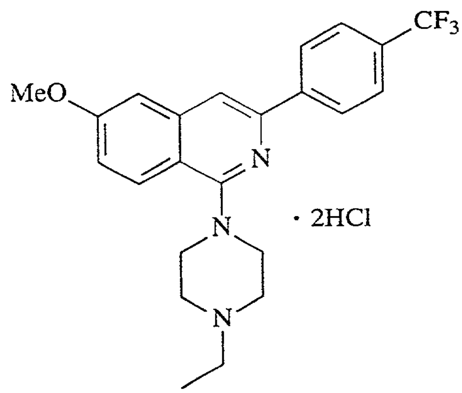
Hydrochloride:

m.p.; 219-221°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.31(3H,t,J=7.2Hz), 2.49(3H,s), 3.19(1H,q,J=7.2Hz), 3.21(1H,q,J=7.2Hz), 3.29(1H,t,J=10.4Hz), 3.32(1H,t,J=10.4Hz), 3.50(2H,t,J=13.6Hz), 3.59(2H,d,J=10.4Hz), 3.80(3H,s), 3.94(2H,d,J=13.6Hz), 7.04(2H,d,J=8.8Hz), 7.38(1H,dd,J=8.8Hz,1.6Hz), 7.70(1H,s), 7.86(1H,s), 7.97(1H,d,J=8.8Hz), 8.11(2H,d,J=8.8Hz), 11.05(1H,br-s).

ESI-Mass; 362(MH^+).

Example 226 Synthesis of 1-(4-ethylpiperazin-1-yl)-6-methoxy-3-(4-trifluoromethylphenyl)isoquinoline dihydrochloride



6-Methoxy-3-(4-trifluoromethylphenyl)isoquinolin-1-one obtained by reacting N-methyl-4-methoxy-2-methylbenzamide (1.0 g) and 4-trifluoromethylbenzonitrile (0.96 g) according to Exampel 10-1 was reacted with phosphorus oxychloride (10 ml) according to Example 10-2, to give 1-chloro-6-methoxy-3-(4-trifluoromethylphenyl)isoquinoline dihydrochloride.

Subsequently, the resulting compound was reacted with N-ethylpiperazine (15 ml) at 100°C for 6 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the free compound of the title compound as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=8.0Hz,3H), 2.57(q,J=8.0Hz,2H), 2.76(m,4H), 3.56(m,4H), 3.95(s,3H), 7.08-7.14(m,2H), 7.65(s,1H), 7.71(d,J=8.4Hz,2H), 7.99(d,J=8.0Hz,1H), 8.25(d,J=8.4Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 0.20 g of the title compound as a yellow powder.

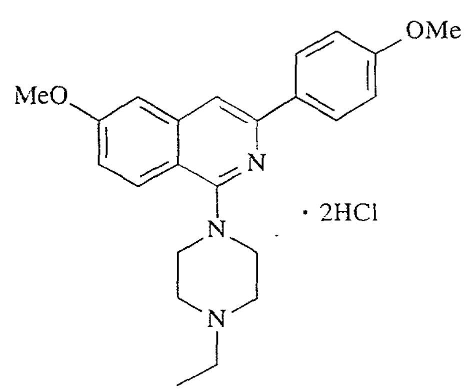
Hydrochloride:

m.p.; 232-233°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.32(t,J=7.2Hz,3H), 3.20-3.28(m,2H), 3.29-3.41(m,2H), 3.41-3.52(m,2H), 3.58-3.82(m,2H), 3.94(s,3H), 3.93-4.01(m,2H), 7.27(dd,J=9.2,2.4Hz,1H), 7.45(d,J=2.4Hz,1H), 7.88(d,J=8.0Hz,1H), 8.07(d,J=9.2Hz,1H), 8.16(s,1H), 8.39(d,J=8.0Hz,1H).

MS(FAB) m/z 386$(M+H)^+$.

Example 227 Synthesis of 1-(4-ethylpiperazin-1-yl)-6-methoxy-3-(4-methoxyphenyl)isoquinoline dihydrochloride



6-Methoxy-3-(4-methoxyphenyl)isoquinolin-1-one (0.40 g) obtained by reacting N-methyl-4-methoxy-2-methylbenzamide (1.0 g) and 4-methoxybenzonitrile (0.75 g) according to Example 10-1 was reacted with phosphorus oxychloride (10 ml) according to Example 10-2, to give 1-chloro-6-methoxy-3-(4-methoxyphenyl)isoquinoline.

Subsequently, the resulting compound was reacted with N-ethylpiperazine (10 ml) at 120°C for 5 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the free compound of the title compound was obtained as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=8.0Hz,3H), 2.56(q,J=8.0Hz,2H), 2.76(m,4H), 3.56(m,4H), 3.86(s,3H), 3.92(s,3H), 6.99(t,J=9.2Hz,2H), 7.32(m,2H), 7.54(s,1H), 7.95(d,J=9.4Hz,1H), 8.10(d,J=9.2Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 86 mg of the title compound as a yellow powder.

Hydrochloride:

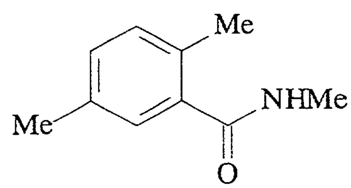
m.p.; 218-220°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.32(t,J=7.2Hz,3H), 3.19-3.28(m,2H), 3.28-3.39(m,2H), 3.40-3.51(m,2H), 3.54-3.70(m,2H), 3.83(s,3H), 3.92(s,3H), 3.90-3.98(m,2H), 7.07(d,J=9.0Hz,2H), 7.17(dd,J=8.8,2.4Hz,1H), 7.36(d,J=2.4Hz,1H), 7.91(s,1H), 8.00(d,J=8.8Hz,1H), 8.12(d,J=9.0Hz,2H), 10.58(br-s,1H).

MS(FAB) m/z 378$(M+H)^+$.

Example 228 Synthesis of 1-(1-ethylpiperazin-4-yl)-7-methyl-3-(4-methoxyphenyl)isoquinoline dihydrochloride

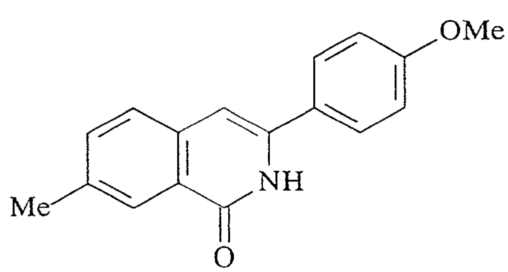
(228-1) 2,5-Dimethyl-N-methylbenzamide



In the same manner as in Example 225-1, the title compound was obtained as a colorless solid (9.656 g, yield; 88%) from 2,5-dimethylbenzoic acid (10.083 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 2.31(3H,s), 2.39(3H,s), 2.99(3H,d,4.8Hz), 5.72(1H,br-s), 7.10(2H,s), 7.26(1H,s).

(228-2) 7-Methyl-3-(4-methoxyphenyl)isoquinolin-1-(2H)-one

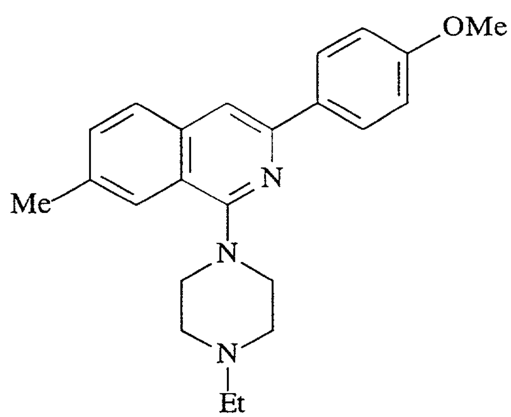


In the same manner as in Example 10-1, the title compound was obtained as a pale yellow solid (1.053 g, yield; 13%) from

2,5-dimethyl-N-methylbenzamide (5.002 g) and anisonitrile (4.128 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 2.50(3H,s), 3.88(3H,s), 6.68(1H,s), 7.02(2H,d,J=8.8Hz), 7.49(1H,d,J=1.2Hz), 8.20(1H,s), 9.41(1H,br-s).

(228-3) 1-(1-Ethylpiperazin-4-yl)-7-methyl-3-(4-methoxyphenyl)isoquinoline dihydrochloride



7-Methyl-3-(4-methoxyphenyl)isoquinolin-1-(2H)-one (1.053 mg) was treated in the same manner as in Example 252-3, to give the hydrochloride of the title compound as yellow crystals (recrystallized in ethanol/isopropyl ether) (1.085 g, yield; 63%).

Hydrochloride:

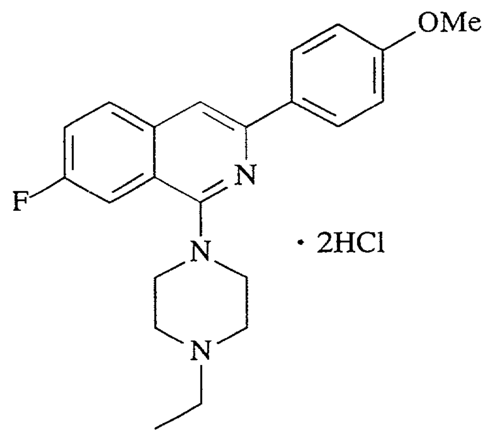
m.p.; 243-246°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.32(3H,t,J=7.2Hz), 2.51(3H,s), 3.20(1H,q,J=7.2Hz), 3.22(1H,q,J=7.2Hz), 3.32(1H,t,J=11.6Hz), 3.35(1H,t,J=11.6Hz), 3.49(2H,t,J=13.6Hz), 3.60(2H,d,J=11.6Hz), 3.93(2H,d,J=13.6Hz), 3.80(3H,s), 7.04(2H,d,J=8.8Hz), 7.55(1H,dd,J=8.4Hz,1.2Hz),

7.83(1H,d,J=1.2Hz), 7.84(1H,d,J=8.4Hz), 7.94(1H,s), 8.11(2H,d,J=8.8Hz), 11.00(1H,br-s).

ESI-Mass; 362(MH^+).

Example 229 Synthesis of 1-(4-ethylpiperazin-1-yl)-7-fluoro-3-(4-methoxyphenyl)isoquinoline dihydrochloride



From starting materials 4-ethynylanisole (12.5 g) and 2-bromo-5-fluorobenzaldehyde (2.15 g), 2.67 g of the free compound of the title compound was obtained according to Example 231.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.20Hz,3H), 2.56(q,J=7.20Hz,2H), 2.80-2.70(br,4H), 3.57-3.50(br,4H), 3.87(s,3H), 7.00(d,J=8.80Hz,2H), 7.38-7.33(m,1H), 7.61(s,1H), 7.69-7.66(m,1H), 7.79-7.775(m,1H), 8.10(d,J=8.8Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give the title compound as a yellow powder.

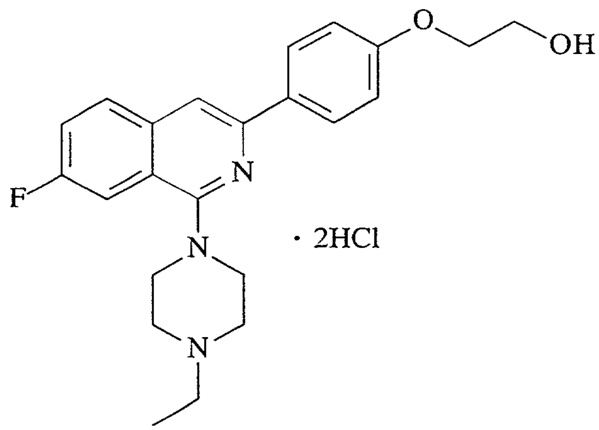
Hydrochloride:

m.p.; 220-225°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 3.60-3.20(m,8H), 3.81(s,3H), 3.94-3.90(m,2H), 7.06(d,J=9.00Hz,2H), 7.68-7.62(m,1H), 7.82-7.76(m,1H), 8.07-8.01(m,2H), 8.12(d,J=9.00Hz,2H).

MS(FAB) m/z 366.00(M+H)$^{+}$.

Example 230 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxyethoxy)phenyl]-7-fluoroisoquinoline dihydrochloride



1-(4-Ethylpiperazin-1-yl)-7-fluoro-3-(4-methoxyphenyl)isoquinoline obtained in Example 229 was converted into the free compound of the title compound in the same manners as in Examples 7 and 36.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.57(q,J=7.2Hz,2H), 2.82-2.70(m,4H), 3.58-3.48(m,4H), 4.03-3.98(m,2H), 4.18-4.14(m,2H), 7.02(d,J=8.8Hz,2H), 7.39-7.33(m,1H), 7.62(s,1H), 7.69-7.65(m,1H), 7.80-7.75(m,1H), 8.10(d,J=8.8Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 0.57 g of the title compound as a yellow

powder.

Hydrochloride:

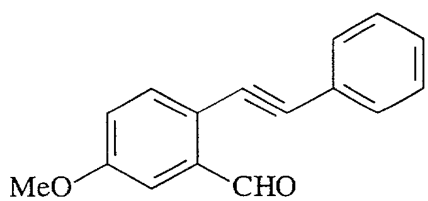
m.p.; 225-229°C

^{1}H-NMR(400MHz,DMSO-d_6); δ(ppm) 1.31(t,J=7.3Hz,3H), 3.29-3.17(m,2H), 3.64-3.30(m,6H), 3.76-3.71(m,2H), 3.96-3.87(m,2H), 4.06-4.01(m,2H), 7.06(d,J=9.00Hz,2H), 7.68-7.62(m,1H), 7.81-7.76(m,1H), 8.07-8.01(m,2H), 8.11(d,J=9.00Hz,2H), 10.79-10.66(m,1H).

MS(FAB) m/z 396.00(M+H)$^+$.

Example 231 Synthesis of 1-(4-ethylpiperazin-1-yl)-7-methoxy-3-phenylisoquinoline dihydrochloride

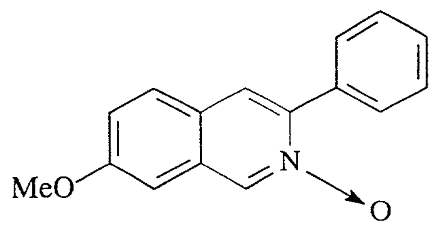
(231-1) 2-(2-Phenylethynyl)-5-methoxybenzaldehyde



Phenylacetylene (2.04 g) and 2-bromo-5-methoxybenzaldehyde (2.15 g) was reacted in dimethylformamide (10 ml) in the presence of dichloro-bis-triphenylphosphine palladium (0.3 g), cuprous iodide (0.15 g) and triethylamine (2 ml) in nitrogen atmosphere at 50°C for 6 hr. The resulting solution was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane

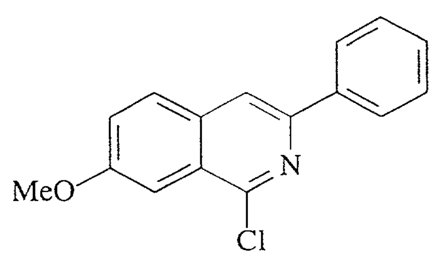
system), to give the hydrochloride of the title compound as a pale yellow oil (0.48 g, yield; 20%).

(231-2) 7-Methoxy-3-phenylisoquinoline-2-oxide



2-(2-Phenylethynyl)-5-methoxybenzaldehyde (0.48 g) was reacted with hydroxylamine hydrochloride (0.17 g) and sodium acetate (0.21 g) in ethanol (10 ml) at 60°C for 2 hr. Potassium carbonate (0.3 g) and water (1 ml) were added to the reaction mixture, and it was heated under reflux for 12 hr. The reaction solution was evaporated. The resulting residue was extracted with methylene chloride, and then washed with brine and dried. The solvent was removed, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.30 g of the title compound as a yellowish brown amorphous.

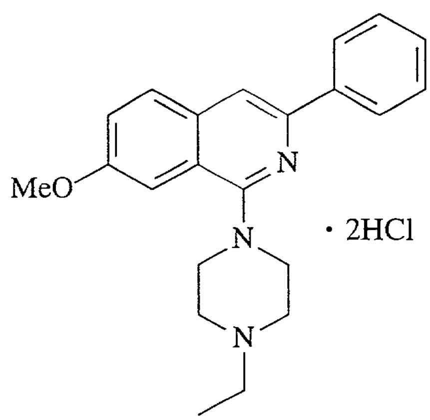
(231-3) 1-Chloro-7-methoxy-3-phenylisoquinoline



7-Methoxy-3-phenylisoquinoline-2-oxide (0.30 g) was reacted with phosphorus oxychloride (3 ml) at 110°C for 2 hr.

The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and an aqueous solution of saturated sodium bicarbonate. The resulting organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give 0.20 g of the title compound was obtained as a white solid.

(231-4) 1-(4-Ethylpiperazin-1-yl)-7-methoxy-3-phenylisoquinoline dihydrochloride



1-Chloro-7-methoxy-3-phenylisoquinoline (0.20 g) was reacted with N-ethylpiperazine (3 ml) and potassium carbonate (0.2 g) at 120°C for 5 hr. To the reaction solution were added ethyl acetate and water, and it was extracted with ethyl acetate. The resulting organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.18 g of the free compound of the title compound as a pale yellow

oil.

Free compound:

^{1}H-NMR(400MHz, $CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.77(m,4H), 3.56(m,4H), 3.95(s,3H), 7.23-7.29(m,1H), 7.32-7.40(m,1H), 7.42-7.48(m,2H), 7.68(s,1H), 7.73(d,J=7.6Hz,1H), 8.15(br-d,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/ether, to give 0.18 g of the title compound as a yellow powder.

Hydrochloride:

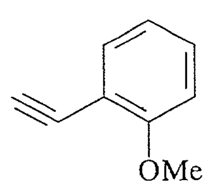
m.p.; 130-132°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.32(t,J=7.2Hz,3H), 3.19-3.28(m,2H), 3.36(q,J=7.2Hz,2H), 3.51(br-t,2H), 3.62(br-d,2H), 3.96(s,3H), 3.93-4.01(m,2H), 7.33(d,J=2.4Hz,1H), 7.37-7.43(m,1H), 7.44(dd,J=9.0,2.4Hz,1H), 7.48-7.53(m,2H), 7.96(d,J=9.0Hz,1H), 8.08(s,1H), 8.16-8.20(m,1H), 10.96(br-s,1H).

MS(FAB) m/z 348$(M+H)^+$.

Example 232 Synthesis of 1-(4-ethylpiperazin-1-yl)-7-methoxy-3-(2-methoxyphenyl)isoquinoline dihydrochloride

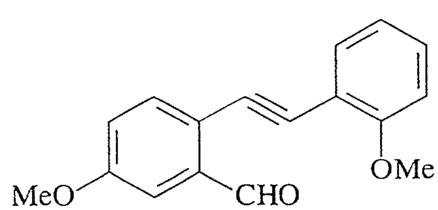
(232-1) 2-Ethynylanisole



2-Iodoanisole (10.5 g) and trimethylsilylacetylene (10.3

g) were reacted in dimethylformamide (50 ml), in the presence of dichloro-bis-triphenylphosphine palladium (1.0 g), cuprous iodide (0.5 g) and triethylamine (15 ml) in nitrogen atmosphere at 50°C for 12 hr. The resulting reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was dissolved in methanol (100 ml), a 5N aqueous solution of sodium hydroxide (20 ml) was added thereto, and then reacted at 60°C for 1 hr. The reaction solution was evaporated, and to the resulting residue were added ether and water. The resulting ether layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a pale yellow oil (3.02 g, yield; 51%).

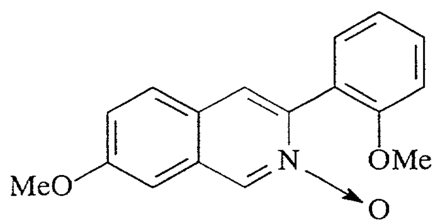
(232-2) 2-[2-(2-Methoxyphenyl)ethynyl]-5-methoxybenzaldehyde



The resulting 2-ethynylanisole (0.79 g) and 2-bromo-5-methoxybenzaldehyde (1.14 g) were reacted in dimethylformamide (50 ml) in the presence of dichloro-bis-

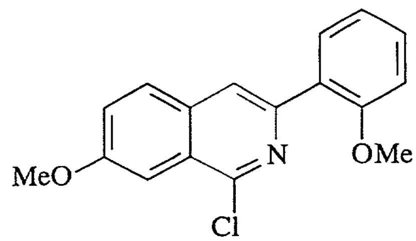
triphenylphosphine palladium (1.0 g), cuprous iodide (0.5 g) and triethylamine (15 ml), in nitrogen atmosphere at 50°C for 6 hr. The resulting reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give 0.95 g of the title compound as a pale yellow oil.

(232-3) 7-Methoxy-3-(2-methoxyphenyl)isoquinoline-2-oxide



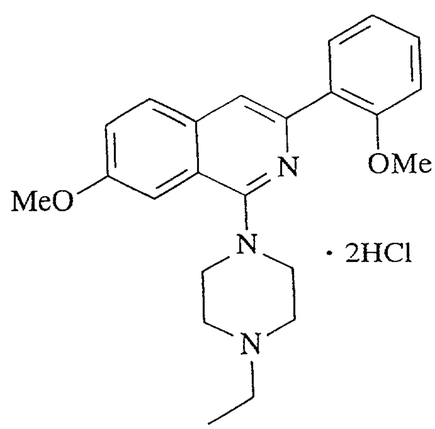
2-[2-(2-Methoxyphenyl)ethynyl]-5-methoxybenzaldehyde (0.95 g), hydroxylamine hydrochloride (0.25 g) and sodium acetate (0.32 g) were reacted in ethanol (20 ml) at 60°C for 2 hr. Potassium carbonate (0.6 g) and water (2 ml) were added to the reaction mixture, and the mixture was heated under reflux for 12 hr. The reaction solution was evaporated, and then the resulting residue was extracted with methylene chloride, washed with brine and dried. The solvent was removed, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.60 g of the title compound as a yellowish brown amorphous.

(232-4) 1-Chloro-7-methoxy-3-(2-methoxyphenyl)isoquinoline



7-Methoxy-3-(2-methoxyphenyl)isoquinoline-2-oxide (0.60 g) and phosphorus oxychloride (5 ml) were reacted at 110°C for 2 hr. The reaction solution was concentrated, and to the resulting residue were added ethyl acetate and an aqueous saturated sodium bicarbonate. The resulting organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give 0.56 g of the title compound as a white solid.

(232-5) 1-(4-Ethylpiperazin-1-yl)-7-methoxy-3-(2-methoxyphenyl)isoquinoline dihydrochloride



1-Chloro-7-methoxy-3-(2-methoxyphenyl)isoquinoline (0.56 g) was reacted with N-ethylpiperazine (5 ml) and potassium carbonate (0.5 g) at 120°C for 5 hr. To the resulting reaction

solution were added ethyl acetate and water, and then it was extracted with ethyl acetate. The resulting organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.43 g of the free compound of the title compound as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.76(m,4H), 3.52(m,4H), 3.92(s,3H), 3.94(s,3H), 7.02(d,J=8.0Hz,1H), 7.09(t,J=8.0Hz,1H), 7.22-7.27(m,1H), 7.30(br-t,1H), 7.38(br-s,1H), 7.71(d,J=8.8Hz,1H), 7.97(s,1H), 8.12(br-d,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/ether, to give 0.32 g of the title compound as a yellow powder.

Hydrochloride:

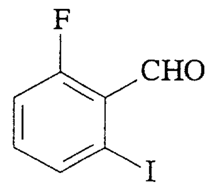
m.p.; 178-179°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 3.18-3.28(m,2H), 3.36(q,J=7.2Hz,2H), 3.43-3.54(m,2H), 3.61(br-d,2H), 3.78-4.00(m,2H), 3.90(s,3H), 3.95(s,3H), 7.10(br-t,1H), 7.17(d,J=8.0Hz,1H), 7.34(d,J=2.4Hz,1H), 7.40(br-t,1H), 7.43(dd,J=8.8,2.4Hz,1H), 7.93(d,J=8.8Hz,1H), 7.99(dd,J=7.6,1.6Hz,1H), 10.89(br-s,1H).

MS(FAB) m/z 378$(M+H)^+$.

Example 233 Synthesis of 1-(1-ethylpiperazin-4-yl)-8-fluoro-3-(4-methoxyphenyl)isoquinoline dihydrochloride

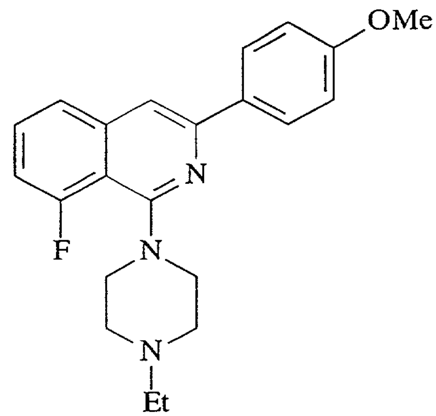
(233-1) 2-Fluoro-6-iodobenzaldehyde



2-Fluoro-6-iodobenzonitrile (10.274 g) was dissolved in toluene (100 ml), followed by the dropwise addition of 1.5M diisobutylaluminium hydride/toluene solution (31 ml) in nitrogen atmosphere at -70°C, and the mixture was stirred for 25 min. Subsequently, it was stirred at room temperature for further 45 min. To the mixture was added 5% sulfuric acid, and it was stirred for 1 hr. Sequentially, the resulting solution was extracted with ethyl acetate, and the resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a yellow oil (8.683 g, yield; 83%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 7.15-7.26(2H,m), 7.82(1H,d,J=7.6Hz), 10.15(1H,s).

(233-2) 1-(1-Ethylpiperazin-4-yl)-8-fluoro-3-(4-methoxyphenyl)isoquinoline dihydrochloride



2-Fluoro-6-iodobenzalhyde (7.012 g) and 4-methoxyphenylacetylene (4.756 g) were treated in the same manner as in Example 139-1, and then the resulting product was treated in the same manner as in Example 251-3 and continuously in the same manner as in Example 251-4, to give 8-fluoro-3-(4-methoxyphenyl)isoquinoline-2-oxide as a grayish black solid (4.566 g). A part (234 mg) of the solid was treated in the same manner as in Example 251-5, to give the hydrochloride of the title compound as yellow crystals (217 mg, yield; 29%).

Hydrochloride:

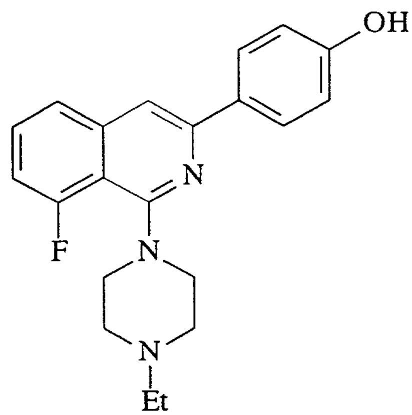
m.p.; 222-227°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.30(3H,t,J=7.2Hz), 3.13-3.24(4H,m), 3.45(2H,t,J=14Hz), 3.60(2H,d,J=11.6Hz), 3.93(2H,d,J=14Hz), 7.06(2H,d,J=8.8Hz), 7.32(1H,ddd,J=12.8Hz,7.9Hz,1Hz), 7.68(1H,ddd,J=8.2Hz,7.9Hz,4.8Hz), 7.76(1H,dd,J=8.2Hz,1Hz), 7.98(1H,d,J=2.4Hz), 8.14(2H,d,J=8.8Hz), 11.00-11.10(1H,br-s).

FAB-Mass; 366(MH^+).

Example 234 Synthesis of 1-(1-ethylpiperazin-4-yl)-8-fluoro-3-[4-(2-hydroxyethoxy)phenyl]isoquinoline dihydrochloride

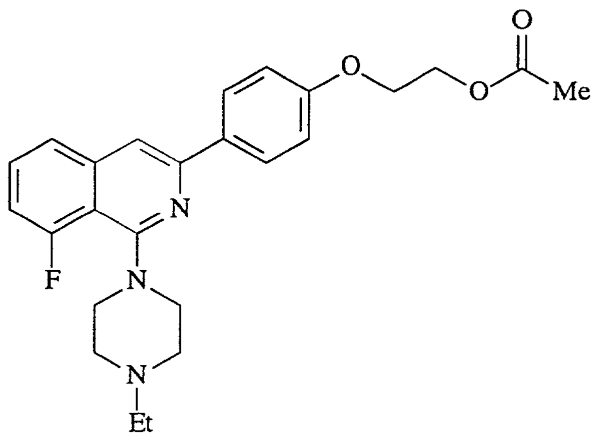
(234-1) 1-(1-Ethylpiperazin-4-yl)-8-fluoro-3-(4-hydroxyphenyl)isoquinoline



In the same manner as in Example 3-1, the title compound was obtained as a yellow solid (1.636 g, yield; 75%) from 1-(1-ethylpiperazin-4-yl)-8-fluoro-3-(4-methoxyphenyl)isoquinoline (2.285 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.22(3H,t,J=7.2Hz), 2.61(2H,q,J=7.2Hz), 2.82(4H,br-s), 3.54(4H,br-s), 6.94(2H,d,J=8.8Hz), 7.05(1H,ddd,J=12.5Hz,7.6Hz,1.2Hz), 7.48(1H,td,J=7.6Hz,4.8Hz), 7.52(1H,dd,J=7.6Hz,1.2Hz), 7.54(1H,s), 8.07(2H,d,J=8.8Hz).

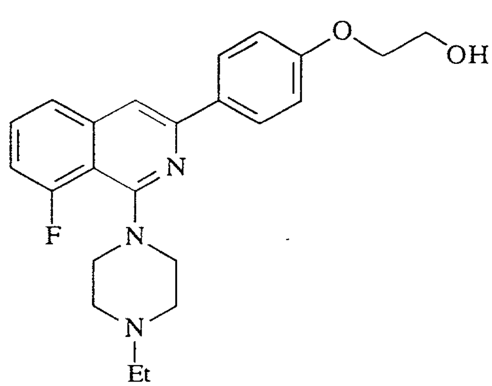
(234-2) 1-(1-Ethylpiperazin-4-yl)-8-fluoro-3-[4-(2-acetoxyethoxy)phenyl]isoquinoline



In the same manner as in Example 300-2, the title compound was obtained as a colorless oil (327 mg, yield; 50%) from 1-(1-ethylpiperazin-4-yl)-8-fluoro-3-(4-hydroxyphenyl)isoquinoline (527 mg) and 2-bromoethyl acetate (188 ml).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(3H,t,J=7.2Hz), 2.12(3H,s), 2.53(2H,q,J=7.2Hz), 2.71(4H,br-s), 3.53(4H,br-s), 4.23(2H,t,J=4.8Hz), 4.45(2H,t,J=4.8Hz), 7.00(2H,d,J=8.8Hz), 7.04(1H,ddd,J=12.5Hz,7.6Hz,1.2Hz), 7.46(1H,td,J=7.6Hz,4.8Hz), 7.51(1H,dd,J=7.6Hz,1.2Hz), 7.52(1H,s), 8.10(2H,d,J=8.8Hz).

(234-3) 1-(1-Ethylpiperazin-4-yl)-8-fluoro-3-[4-(2-hydroxyethoxy)phenyl]isoquinoline dihydrochloride



1-(1-Ethylpiperazin-4-yl)-8-fluoro-3-[4-(2-acetoxyethoxy)phenyl]isoquinoline (527 mg) was dissolved in ethanol (16 ml), followed by the addition of 2N sodium hydroxide (8 ml), and the mixture was stirred at room temperature overnight. The reaction mixture was evaporated, and then it was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by (NH) silica gel column chromatography (ethyl acetate/hexane system). Then, the resulting product was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/isopropyl ether, to give the hydrochloride of the title compound as yellow crystals (343 mg, yield 97%).

Hydrochloride:

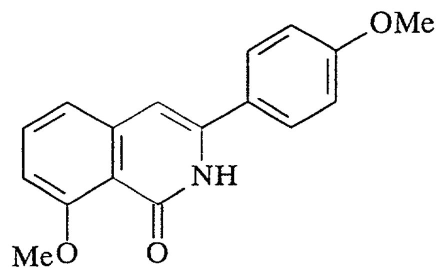
m.p.; 215-219°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.30(3H,t,J=7.2Hz), 3.13-3.25(4H,m), 3.43(2H,t,J=13.6Hz), 3.60(2H,d,J=11.6Hz), 3.73(2H,t,J=5Hz), 3.93(2H,d,J=13.6Hz), 4.04(2H,t,J=5Hz), 7.06(2H,d,J=8.8Hz), 7.31(1H,ddd,J=12.8Hz,7.9Hz,1Hz), 7.67(1H,ddd,J=8.2Hz,7.9Hz,4.8Hz), 7.75(1H,dd,J=8.2Hz,1Hz), 7.98(1H,d,J=2Hz), 8.13(2H,d,J=8.8Hz), 10.85-10.95(1H,br-s).

FAB-Mass; 396(MH^+).

Example 235 Synthesis of 1-(1-ethylpiperazin-4-yl)-8-methoxy-3-(4-methoxyphenyl)isoquinoline dihydrochloride

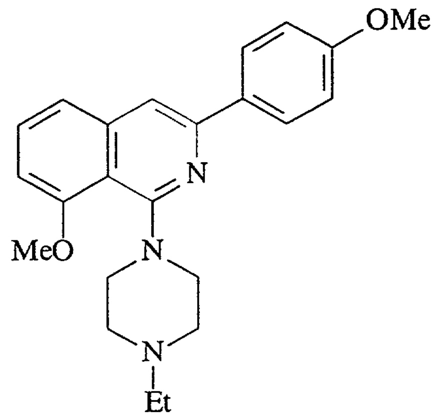
(235-1) 8-Methoxy-3-(4-methoxyphenyl)isoquinolin-1-(2H)-one



Ethyl 2-methoxy-6-methylbenzoate (5.011 g) was dissolved in tetrahydrofuran (20 ml), followed by the addition of 1.5M lithium diisopropylamide/cyclohexane solution (19 ml) in nitrogen atmosphere at -70°C. The resulting mixture was stirred for 45 min. Anisonitrile (3.462 g)/tetrahydrofuran (10 ml) solution was added to the reaction mixture. The cooling bath was removed, and then the mixture was stirred for 100 min. An aqueous solution of saturated ammonium chloride and ethyl acetate were added to the reaction solution, and the mixture was stirred for 30 min. The resulting insoluble matters were collected by filtration, and then washed with ethyl acetate and water, to give the title compound as a pale yellow solid (991 mg, yield; 13%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 3.87(3H,s), 4.02(3H,s). 6.58(1H,s), 6.93(1H,d,J=7.6Hz), 7.01(2H,d,J=8.8Hz), 7.11(1H,d,J=7.6Hz), 7.52-7.58(3H,m), 8.58(1H,br-s).

(235-2) 1-(1-Ethylpiperazin-4-yl)-8-methoxy-3-(4-methoxyphenyl)isoquinoline dihydrochloride



8-Methoxy-3-(4-methoxyphenyl)isoquinolin-1-(2H)-one (991 mg) was treated in the same manner as in Example 252-3, to give the hydrochloride of the title compound as colorless crystals (recrystallized from 10% hydrous ethanol/isopropyl ether) (1.115 g, yield; 71%).

Hydrochloride:

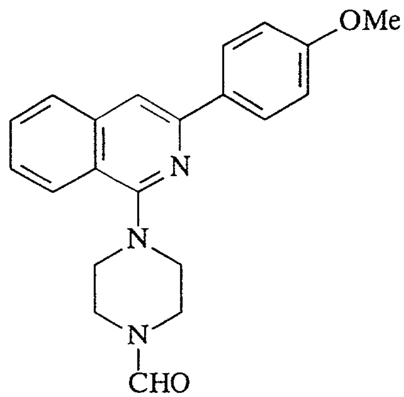
m.p.; 237-241°C

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.30(3H,t,J=7.2Hz), 3.12-3.36(6H,m), 3.59(2H,d,J=10.4Hz), 3.91(2H,d,J=12.4Hz), 7.02(1H,d,J=8Hz), 7.04(2H,d,J=8.8Hz), 7.44(1H,d,J=8Hz), 7.58(1H,t,J=8Hz), 7.82(1H,s), 8.11(2H,d,J=8.8Hz), 10.67(1H,br-s).

ESI-Mass; 378(MH^+).

Example 236 Synthesis of 1-(1-propylpiperazin-4-yl)-3-(4-methoxyphenyl)isoquinoline dihydrochloride

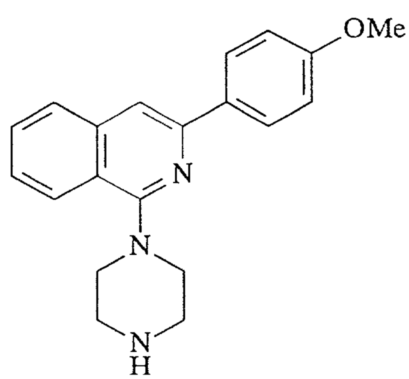
(236-1) 1-(4-Formylpiperazinyl)-3-(4-methoxyphenyl)isoquinoline



In the same manner as in Example 322, the title compound was obtained as a yellow amorphous (4.797 g, yield; 86%) from 1-chloro-3-(4-methoxyphenyl)isoquinoline (4.316 g) and 1-piperazinecarboxyaldehyde (4.6 ml).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 3.47-3.50(2H,m), 7.48(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.61(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.68(1H,s), 7.80(1H,d,J=8Hz), 8.10(2H,d,J=8.8Hz), 8.16(1H,s).

(236-2) 1-Piperazinyl-3-(4-methoxyphenyl)isoquinoline

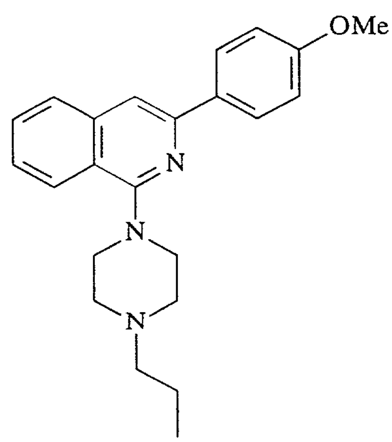


1-(4-Formylpiperazinyl)-3-(4-methoxyphenyl)isoquinoline (4.797 g) was dissolved in ethanol (85 ml), followed by the addition of 2N sodium hydroxide (35 ml), and the mixture was heated under reflux for 4 hr. The

reaction mixture was evaporated, water was added thereto, and extracted with chloroform. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by (NH) silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a colorless solid (2.720 g, yield; 63%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 3.16-3.19(4H,m), 3.47-3.51(4H,m), 3.88(3H,s), 7.01(2H,d,J=8.8Hz), 7.44(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.57(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.77(1H,d,J=8Hz), 8.07(1H,d,J=8Hz), 8.12(2H,d,J=8.8Hz).

(236-3) 1-(1-Propylpiperazin-4-yl)-3-(4-methoxyphenyl)isoquinoline dihydrochloride



1-Piperazinyl-3-(4-methoxyphenyl)isoquinoline (319 mg) was dissolved in N,N-dimethylformamide (3 ml), followed by the addition of 1-bromopropane (91 ml) and triethylamine (167 ml), and the mixture was stirred at 50°C overnight. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by

silica gel column chromatography (methylene chloride/methanol system). Then, the resulting product was converted into a hydrochloride in a conventional manner and recrystallized from ethanol/isopropyl ether, to give the hydrochloride of the title compound as yellow crystals (380 mg, yield; 90%).

Hydrochloride:

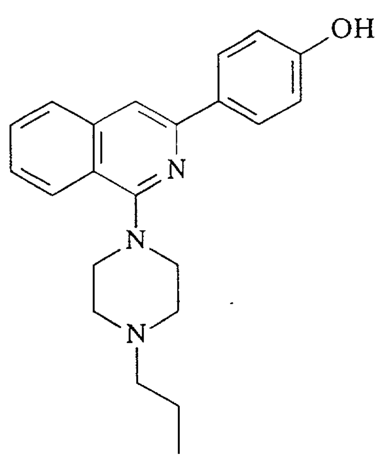
m.p.; 220-226°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.93(3H,t,J=7.2Hz), 1.72-1.82(2H,m), 3.07-3.13(2H,m), 3.32(1H,t,J=11Hz), 3.35(1H,t,J=11Hz), 3.52(2H,t,J=14Hz), 3.60(2H,d,J=11Hz), 3.81(3H,s), 3.95(2H,d,J=14Hz), 7.05(2H,d,J=8.8Hz), 7.55(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.70(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.93(1H,d,J=8Hz), 7.97(1H,s), 8.07(1H,d,J=8Hz), 8.13(2H,d,J=8.8Hz), 10.93(1H,br-s).

ESI-Mass; 362(MH^+).

<u>Example 237</u> <u>Synthesis of 1-(1-propylpiperazin-4-yl)-3-[4-(2-hydroxyethoxy)phenyl]isoquinoline dihydrochloride</u>

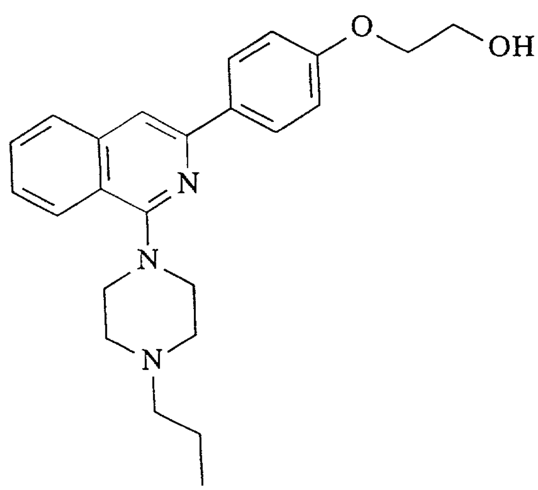
<u>(237-1)</u> <u>1-(1-Propylpiperazin-4-yl)-3-(4-hydroxyphenyl)isoquinoline</u>



In the same manner as in Example 3-1, the title compound was obtained as a pale brown solid (853 mg, yield; 78%) from 1-(1-propylpiperazin-4-yl)-3-(4-methoxyphenyl)isoquinoline (1.147 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.97(3H,t,J=7.6Hz), 1.56-1.66(2H,m), 2.43-2.48(2H,m), 2.77(4H,t,J=4.4Hz), 3.57(4H,t,J=4.4Hz), 6.93(2H,d,J=8.8Hz), 7.43(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.57(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.61(1H,s), 7.76(1H,d,J=8Hz), 8.08(2H,d,J=8.8Hz).

(237-2) 1-(1-Propylpiperazin-4-yl)-3-[4-(2-hydroxyethoxy)phenyl]isoquinoline dihydrochloride



1-(1-Propylpiperazin-4-yl)-3-(4-hydroxyphenyl)isoquinoline (853 mg) was dissolved in N,N-dimethylformamide (12 ml), followed by the addition of 60% sodium hydride (120 mg) under ice-cooling, and the mixture was stirred at room temperature for 1 hr. The reaction solution was ice-cooled again, followed by the addition of (2-bromoethoxy)-t-butyldimethylsilane (718 mg), and the mixture

was stirred overnight. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was dissolved in tetrahydrofuran (10 ml). To the mixture, 1.0M tetrabutylammonium fluoride/tetrahydrofuran solution (2.8 ml) was added under ice-cooling. The resulting mixture was stirred, as it was, at room temperature for 1 hr. The reaction mixture was evaporated, and then purified by silica gel column chromatography (methylene chloride/methanol system). Sequentially, the resulting product was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/isopropyl ether, to give the hydrochloride of the title compound as yellow crystals (485 mg, yield; 40%).

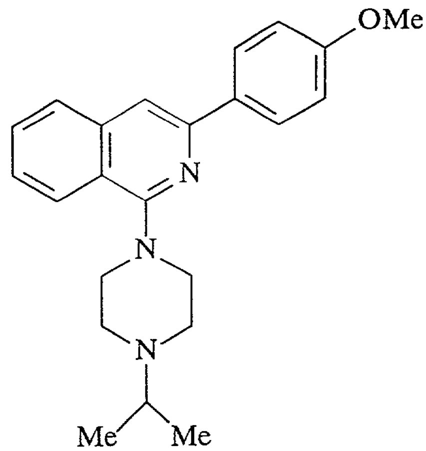
Hydrochloride:

m.p.; 220-225°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.93(3H,t,J=7.6Hz), 1.72-1.82(2H,m), 3.07-3.15(2H,m), 3.33(1H,t,J=10.6Hz), 3.36(1H,t,J=10.6Hz), 3.51(2H,t,J=13.6Hz), 3.60(2H,d,J=10.6Hz), 3.73(2H,t,J=5Hz), 3.95(2H,d,J=13.6Hz), 4.04(2H,t,J=5Hz), 7.05(2H,d,J=8.8Hz), 7.55(1H,ddd,J=8.4Hz,7Hz,1.2Hz), 7.70(1H,ddd,J=8.4Hz,7Hz,1.2Hz), 7.93(1H,d,J=8.4Hz), 7.97(1H,s), 8.07(1H,d,J=8.4Hz), 8.12(2H,d,J=8.8Hz), 10.88(1H,br-s).

ESI-Mass; 392(MH^+).

Example 238 Synthesis of 1-(1-isopropylpiperazin-4-yl)-3-(4-methoxyphenyl)isoquinoline dihydrochloride



In the same manner as in Example 236, the hydrochloride of the title compound was obtained as pale brown crystals (recrystalized from ethanol/isopropyl ether) (189 mg, yield; 80%) from 1-piperazinyl-3-(4-methoxyphenyl)isoquinoline (160 mg) and 2-bromopropane (470 ml).

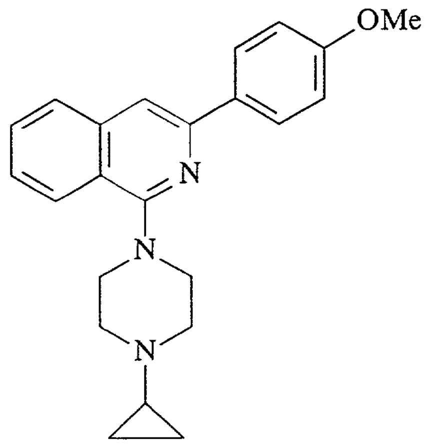
Hydrochloride:

m.p.; 220°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.35(6H,d,J=6.8Hz), 3.36(1H,t,J=10Hz), 3.39(1H,t,J=10Hz), 3.48-3.64(5H,m), 3.94(2H,d,J=13.6Hz), 7.04(2H,d,J=8.8Hz), 7.54(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.69(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.92(1H,d,J=8Hz), 7.97(1H,s), 8.11(1H,d,J=8Hz), 8.13(2H,d,J=8.8Hz), 11.14(1H,br-s).

ESI-Mass; 362(MH$^+$).

Example 239 Synthesis of 1-(1-cyclopropylpiperazin-4-yl)-3-(4-methoxyphenyl)isoquinoline dihydrochloride



1-Chloro-3-(4-methoxyphenyl)isoquinoline (514 mg), and 1-cyclopropylpiperazine hydrochloride salt (378 mg) described in JP-A 62-129273 were dissolved in dimethyl sulfoxide (7 ml), followed by the addition of potassium carbonate (788 mg), and the resulting mixture was stirred at 100°C overnight. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system). The resulting product was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/isopropyl ether, to give the hydrochloride of the title compound as yellow crystals (136 mg, yield; 16%).

Hydrochloride:

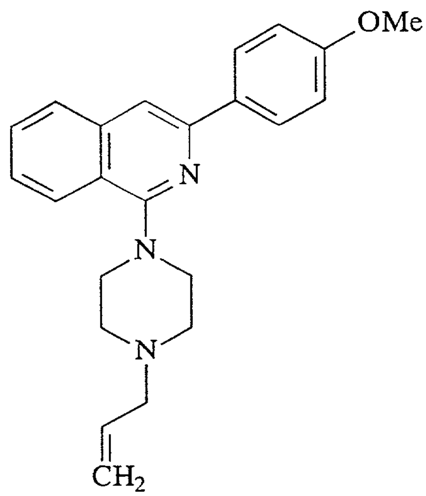
m.p.; 138-143°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.80-0.88(4H,br-q), 1.18-1.22(4H,br-q), 2.93-3.02(1H,m), 3.48-3.63(6H,m), 3.80(3H,s), 3.92-3.98(2H,d,J=9.6Hz), 7.04(2H,d,J=8.8Hz),

7.55(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.69(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.93(1H,d,J=8Hz), 7.97(1H,s), 8.07(1H,d,J=8Hz), 8.13(2H,d,J=8.8Hz), 11.08(1H,br-s).

ESI-Mass; 360(MH^+).

Example 240 Synthesis of 1-(1-allylpiperazin-4-yl)-3-(4-methoxyphenyl)isoquinoline dihydrochloride



In the same manner as in Example 236, the hydrochloride of the title compound was obtained as yellow crystals (recrystalized from ethanol) (364 mg, yield; 80%) from 1-piperazinyl-3-(4-methoxyphenyl)isoquinoline (319 mg) and allyl bromide (87 ml).

Hydrochloride:

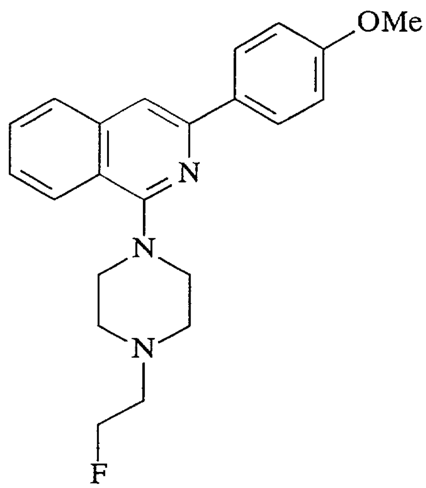
m.p.; 111-116°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 3.28-3.38(2H,m), 3.45-3.58(4H,m), 3.81(3H,s), 3.82-3.88(2H,br-t), 3.96(2H,d,J=14Hz), 5.50-5.60(2H,m), 6.00-6.12(1H,m), 7.05(2H,d,J=8.8Hz), 7.55(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.70(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.93(1H,d,J=8.8Hz),

7.97(1H,s), 8.07(1H,d,J=8Hz), 8.13(2H,d,J=8.8Hz), 11.31(1H,br-s).

ESI-Mass; 360(MH^+).

Example 241 Synthesis of 1-[1-(2-fluoroethyl)piperazin-4-yl]-3-(4-methoxyphenyl)isoquinoline dihydrochloride



In the same manner as in Example 236, the hydrochloride of the title compound was obtained as yellow crystals (recrystallized from ethanol) (355 mg, yield; 80%) from 1-piperazinyl-3-(4-methoxyphenyl)isoquinoline (319 mg) and 1-bromo-2-fluoroethane (74 ml).

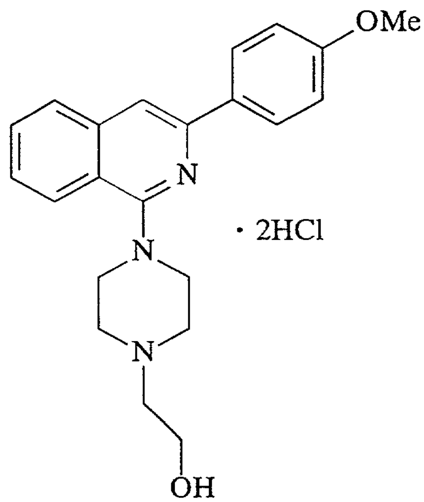
Hydrochloride:

m.p.; 120-124°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 3.44-3.68(8H,m), 3.81(3H,s), 3.98(2H,d,J=12Hz), 4.91(1H,t,J=4.2Hz), 5.02(1H,t,J=4.2Hz), 7.05(2H,d,J=8.8Hz), 7.55(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.70(1H,ddd,J=8Hz,7Hz,1.2Hz), 7:93(1H,d,J=8Hz), 7.98(1H,s), 8.08(1H,d,J=8Hz), 8.13(2H,d,J=8Hz), 11.35(1H,br-s).

ESI-Mass; 362(MH^+).

Example 242 Synthesis of 1-[4-(2-hydroxyethyl)piperazin-1-yl]-3-(4-methoxyphenyl)isoquinoline dihydrochloride



A mixture of 1-chloro-3-(4-methoxyphenyl)isoquinoline (0.79 g) obtained in Example 10-2, 1-(2-hydroxyethyl)piperazine (0.6 g), and potassium carbonate (0.83 g) was reacted in dimethylformamide (10 ml) at 100°C for 6 hr. The reaction mixture solution was evaporated. Ethyl acetate and water were added to the resulting residue. The resulting organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the free compound of the title compound as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 3.87(s,3H), 7.02(d,J=8.4Hz,2H), 7.61(br-t,1H), 7.71(br-t,1H), 7.84(d,J=8.0Hz,1H), 7.92(s,1H), 8.07(d,J=8.4Hz,2H), 8.32(d,J=8.0Hz,1H).

The resulting free compound was converted into a

hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 0.48 g of the title compound as a yellow powder.

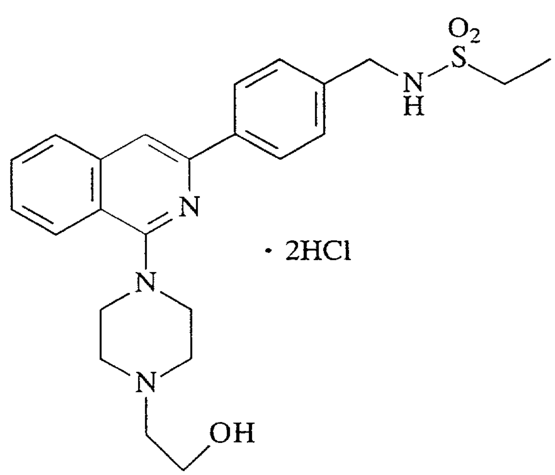
Hydrochloride:

m.p.; 163-165°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 3.27(m,2H), 3.42(t,J=11.0Hz,2H), 3.53(t,J=11.0Hz,2H), 3.65(d,J=11.0Hz,2H), 3.80(s,3H), 3.82(m,2H), 3.94(d,J=11.0Hz,2H), 7.05(d,J=8.4Hz,2H), 7.55(t,J=8.0Hz,1H), 7.70(t,J=8.0Hz,1H), 7.92(d,J=8.0Hz,1H), 7.97(s,1H), 8.06(t,J=8.0Hz,1H), 8.13(d,J=8.4Hz,2H), 10.68(m,1H).

MS(FAB) m/z 364(M+H)$^+$.

Example 243 Synthesis of 3-(4-ethylsulfonylaminomethylphenyl)-1-[4-(2-hydroxyethyl)piperazin-1-yl]isoquinoline hydrochloride



The free compound of the title compound was obtained (118 mg, yield; 62%) from 1-chloro-3-(4-ethylsulfonylaminomethylphenyl)isoquinoline (152 mg) and 4-

hydroxyethylpiperazine (1 ml) in the same manner as in Example 10. The resulting free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 171-174°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.20(t,J=7.2Hz,3H), 2.99(q,J=7.6Hz,2H), 3.30-3.34(m,2H), 3.43-3.52(m,2H), 3.56-3.66(m,2H), 3.70(d,J=11.2Hz,2H), 3.87-3.90(m,2H), 4.01(d,J=12.8Hz,2H), 4.23(d,J=6.0Hz,2H), 7.50(d,J=8.4Hz,2H), 7.62(t,J=8.0Hz,1H), 7.73(br,1H), 7.56(t,J=8.0Hz,1H), 8.00(d,J=8.0Hz,1H), 8.11(s,1H), 8.13(d,J=8.0Hz,1H), 8.20(d,J=8.4Hz,2H).

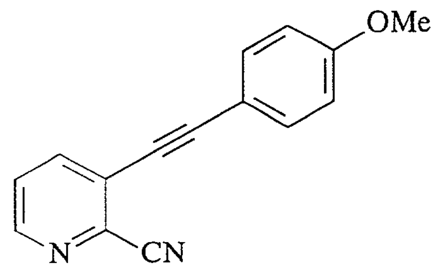
MS(FAB) m/z 455(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.34(t,J=7.6Hz,3H), 2.69(t,J=5.2Hz,2H), 2.82(br,4H), 2.99(q,J=7.2Hz,2H), 3.56(br,4H), 3.69(t,J=5.2Hz,2H), 4.36(d,J=4.4Hz,2H), 4.74(br,1H), 7.44(d,J=8.4Hz,2H), 7.48(ddd,J=8.4,8.0,1.2Hz,1H), 7.60(ddd,J=8.4,8.0,1.2Hz,1H), 7.70(s,1H), 7.79(d,J=8.0Hz,1H), 8.07(d,J=8.4Hz,1H), 8.16(d,J=8.4Hz,2H).

Example 244 Synthesis of 8-(4-ethylpiperazin-1-yl)-6-(4-methoxyphenyl)pyrido[2,3-c]pyridine hydrochloride

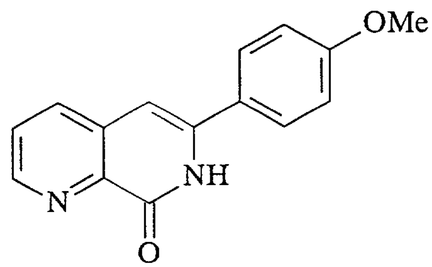
(244-1) 2-Cyano-3-(4-methoxyphenyl)ethynylpyridine



A mixture of 3-bromo-2-cyanopyridine (3.63 g, 19.8 mmol), 4-ethynylanisole (3.15 g, 1.2 equivalents), dichlorobis(triphenylphosphine)palladium (II) (0.28 g, 0.02 equivalent), copper (I) iodide (0.14 g), triethylamine (60 ml) and dry pyridine (6 ml) was heated under reflux in nitrogen atmosphere for 12.5 hr. After the mixture was cooled as it was, ethyl acetate and a 10% aqueous solution of sodium carbonate were added thereto. The resulting mixture was stirred, and the resulting insoluble matters were filtered off. The organic layer was separated and washed with water/brine (1:1(v/v)) and brine in this order, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (n-hexane/ethyl acetate/chloroform/methanol system). The resulting product was recrystallized from chloroform/n-hexane, to give the title compound as a pale yellow powder (3.53 g, yield; 81%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 3.85(s,3 H), 3.92(d,J=9.0Hz,2H), 7.47(dd,J=4.8,8.0Hz,1H), 7.57(d,J=9.0Hz,2H), 7.90(dd,J=1.6,8.0Hz,1H), 8.60(dd,J=1.6,4.8Hz,1H).

(244-2) 6-(4-Methoxyphenyl)-7,8-dihydropyrido[2,3-c]pyridin-8-one



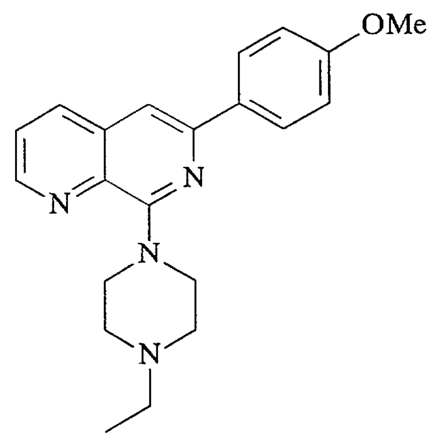
Polyphosphoric acid (45 g) was added to 2-cyano-3-(4-methoxyphenyl)ethynylpyridine (3.07 g, 13.1 mmol), which was then stirred at 110-120°C for 15 min. After cooling as it was, ice was added thereto and the mixture was stirred. Ethyl acetate and sodium carbonate were added thereto, and the pH of the aqueous layer was adjusted to about pH 8. The organic layer was separated and washed with brine, and then dried over magnesium sulfate. The solvent was evaporated, to give 2.43 g of a pale brown powder.

Sodium acetate of 5.88 g was added to the resulting pale brown powder, which was then stirred in a sealed tube at 120°C for 13 hr. After cooled as it was, water was added thereto, and then it was extracted with chloroform. The organic layer was separated and washed with brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system). The resulting product was reprecipitated with chloroform/n-hexane, to give the title compound as a pale brown powder (0.71 g, yield; 21%).

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 3.83(s,3H), 6.83(s,1H), 7.06(d,J=8.8Hz,2H), 7.67(dd,J=4.2,8.2Hz,1H),

7.77(d,J=8.8Hz,2H), 8.11(dd,J=1.6,8.2Hz,1H), 8.72(dd,J=1.6,4.2Hz,1H), 11.71(s,1H).

(244-3) 8-(4-Ethylpiperazin-1-yl)-6-(4-methoxyphenyl)pyrido[2,3-c]pyridine hydrochloride



Phosphorus oxychloride (20 ml) was added to 6-(4-methoxyphenyl)-7,8-dihydropyrido[2,3-c]pyridin-8-one (0.70 g, 2.77 mmol), and the mixture was heated under reflux for 1.5 hr. After cooling as it was, excess phosphorus oxychloride was evaporated. To the resulting residue was added N-ethylpiperazine (35 ml), and the mixture was stirred in nitrogen atmosphere at 100°C for 2 hr. After cooling as it was, the reaction solution was evaporated. The resulting residue was dissolved in ethyl acetate, washed sequentially with a 10% aqueous solution of sodium carbonate, water and brine, and dried over magnesium sulfate. Then, the solvent was evaporated, and the resulting residue was purified by NH-silica gel column chromatography (n-hexane/ethyl acetate system), to give the title compound as pale brown crystals (0.98 g, yield; quantitative).

The resulting compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/diisopropyl ether, to give 0.98 g of the hydrochloride of the title compound.

Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.31(t,J=7.2Hz,3H), 3.16-3.28(m,4H), 3.55-3.65(m,4H), 3.83(s,3H), 5.15(br-d,2H), 7.07(d,J=9.0Hz,2H), 7.70(dd,J=4.2,8.4Hz,1H), 7.85(s,1H), 8.14(d,J=9.0Hz,2H), 8.32(dd,J=1.6,8.4Hz,1H), 8.83(dd,J=1.6,4.2Hz,1H), 10.73(br-s,1H).

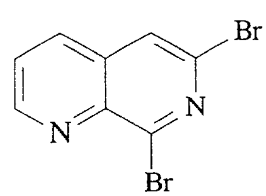
MS(FAB) m/z 349$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.53(q,J=7.2Hz,2H), 2.74(br-t,4H), 3.88(s,3H), 4.15(br-t,4H), 7.01(d,J=8.8Hz,2H), 7.42(s,1H), 7.44(dd,J=4.0,8.0Hz,1H), 8.02(dd,J=1.6,8.0Hz,1H), 8.11(d,J=8.8Hz,2H), 8.75(dd,J=1.6,4.0Hz,1H).

Example 245 Synthesis of 8-(1-ethylpiperazin-4-yl)-6-[4-(2-hydroxyethoxy)phenyl]-1,7-naphthyridine dihydrochloride

(245-1) 6,8-Dibromo-1,7-napthyridine

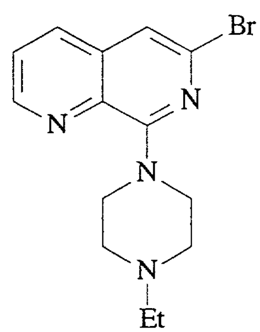


To 6-amino-8-bromo-1,7-naphthyridine (6.554 g) synthesized according to Tetrahedron Letters, 12, 1233, 1966 was added 48% hydrobromic acid (55 ml). Sodium nitrite (4.141

g) was added thereto in small portions under ice-cooling, and the mixture was stirred overnight. The reaction mixture was basified by adding 5N sodium hydroxide thereto, and it was extracted with ethyl acetate. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a yellowish orange solid (2.856 g, yield; 34%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 7.70(1H,dd,J=8.4Hz,4Hz), 8.12(1H,dd,J=8.4Hz,1.6Hz), 9.15(1H,dd,J=4Hz,1.6Hz).

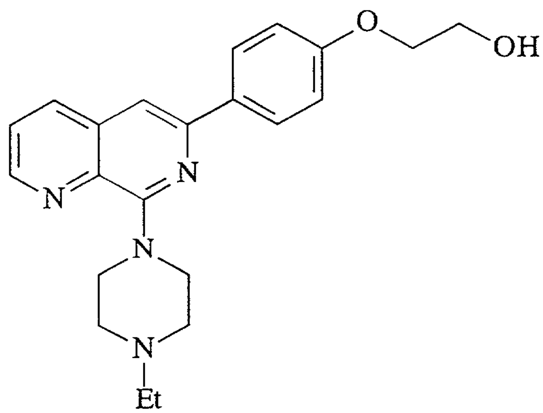
(245-2) 6-Bromo-8-(1-ethylpiperazin-4-yl)-1,7-naphthyridine



6,8-Dibromo-1,7-naphthyridine (3.464 g) was added to 1-ethylpiperazine (10 ml), and the resulting mixture was stirred at 100°C for 15 min. The reaction mixture was evaporated, and then partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by (NH) silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a yellowish orange solid (3.780 g, yield; 98%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.15(3H,t,J=7.2Hz), 2.50(2H,q,J=7.2Hz), 2.67(4H,t,J=5Hz), 4.19(4H,t,J=5Hz), 7.14(1H,s), 7.45(1H,dd,J=8.4Hz,4Hz), 7.88(1H,dd,J=8.4Hz,1.6Hz), 8.75(1H,dd,J=4Hz,1.6Hz).

(245-3) 8-(1-Ethylpiperazin-4-yl)-6-[4-(2-hydroxyethoxy)phenyl]-1,7-naphthyridine dihydrochloride



In the same manner as in Example 300, the hydrochloride of the title compound was obtained as yellow crystals (374 mg, yield; 67%) from 6-bromo-8-(1-ethylpiperazin-4-yl)-1,7-naphthyridine (385 mg) and 4-tributylstannylphenoxyethyl acetate (684 mg).

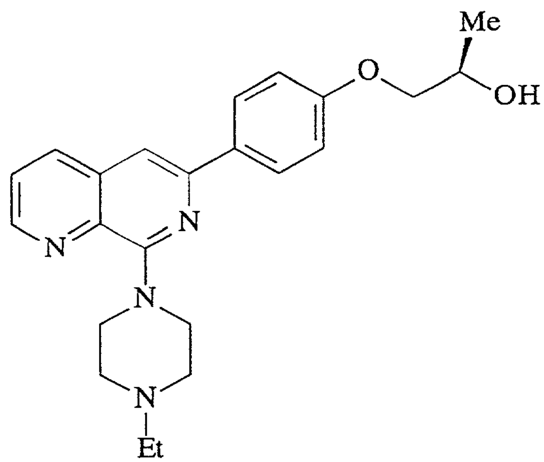
Hydrochloride:

m.p.; 137-143°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.29(3H,t,J=7.2Hz), 3.10-3.26(4H,m), 3.57-3.65(4H.m), 3.73(2H,t,J=5Hz), 4.04(2H,t,J=4Hz), 5.09-5.12(2H,m), 7.05(2H,d,J=8.8Hz), 7.68(1H,dd,J=8.4Hz,4.4Hz), 7.83(1H,s), 8.11(2H,d,J=8.8Hz), 8.30(1H,dd,J=8.4Hz,1.6Hz), 8.81(1H,dd,J=4.4Hz,1.6Hz), 11.05-11.15(1H,br-s).

ESI-Mass; 379(MH^+).

Example 246 Synthesis of 8-(1-ethylpiperazin-4-yl)-6-{4-[(S)-2-hydroxypropoxy]phenyl}-1,7-naphthyridine dihydrochloride



In the same manner as in Example 300, the hydrochloride of the title compound was obtained as a pale yellow amorphous (459 mg, yield; 77%) from 6-bromo-8-(1-ethylpiperazin-4-yl)-1,7-naphthyridine (418 mg) and 2-(4-tributylstannylphenoxy)-(S)-1-methylethyl acetate (1.136 mg).

Hydrochloride:

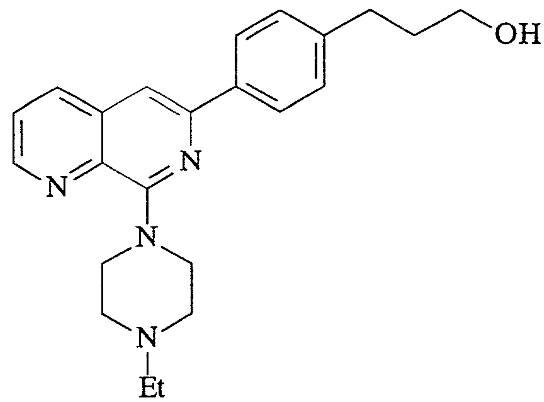
m.p.; 136-140°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.16(3H,d,J=6.4Hz), 1.29(3H,t,J=7.2Hz), 3.16(1H,q,J=7.2Hz), 3.18(1H,q,J=7.2Hz), 3.20(1H,t,J=10.8Hz), 3.23(1H,t,J=10.8Hz), 3.58(2H,t,J=13.6Hz), 3.62(1H,q,J=10.8Hz), 3.82-3.91(2H,m), 3.93-4.00(1H,m), 5.11(2H,d,J=13.6Hz), 7.05(2H,d,J=8.8Hz), 7.68(1H,dd,J=8.4Hz,4.4Hz), 7.83(1H,s), 8.11(2H,d,J=8.8Hz),

8.30(1H,dd,J=8.4Hz,1.6Hz), 8.81(1H,dd,4.4Hz,1.6Hz), 10.85-10.95(1H,br-s).

ESI-Mass; 393(MH^+).

Example 247 Synthesis of 8-(1-ethylpiperazin-4-yl)-6-[4-(3-hydroxypropyl)phenyl]-1,7-naphthyridine dihydrochloride



In the same manner as in Example 167-2, the hydrochloride of the title compound was obtained as yellow crystals (recrystalized from ethanol/isopropyl ether) (352 mg, yield; 62%) from 4-[3-(t-butyldimethylsilyloxy)propyl]-1-bromobenzene (2.035 g) and 6-bromo-8-(1-ethylpiperazin-4-yl)-1,7-naphthyridine (418 mg).

Hydrochloride:

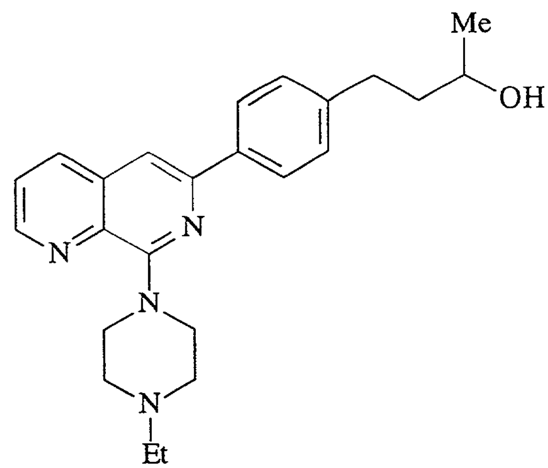
m.p.; 119-122°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.29(3H,t,J=7.2Hz), 1.70-1.78(2H,m), 2.66(2H,t,J=7.6Hz), 3.16(1H,q,J=7.2Hz), 3.18(1H,q,J=7.2Hz), 3.20(1H,t,J=12.4Hz), 3.23(1H,t,J=12.4Hz), 3.43(2H,t,J=6.4Hz), 3.56(2H,t,J=13.6Hz), 3.62(2H,d,J=12.4Hz), 7.31(2H,d,J=8.8Hz), 7.70(1H,dd,J=8.4Hz,4Hz), 7.89(1H,s), 8.08(2H,d,J=8.8Hz), 8.33(1H,dd,J=8.4Hz,1.6Hz),

8.83(1H,dd,J=4Hz,1.6Hz), 10.65-10-75(1H,br-s).

ESI-Mass; 377(MH^+).

<u>Example 248</u> <u>Synthesis of 8-(1-ethylpiperazin-4-yl)-6-[4-(3-hydroxybutyl)phenyl]-1,7-naphthyridine dihydrochloride</u>



In the same manner as in Example 161-3, the hydrochloride of the title compound was obtained as yellow crystals (recrystalized from ethanol/isopropyl ether) (346 mg, yield; 54%) from 4-[3-(t-butyldimethylsilyloxy)butyl]-1-bromobenzene (2.237 g) and 6-bromo-8-(1-ethylpiperazin-4-yl)-1,7-naphthyridine (418 mg).

Hydrochloride:

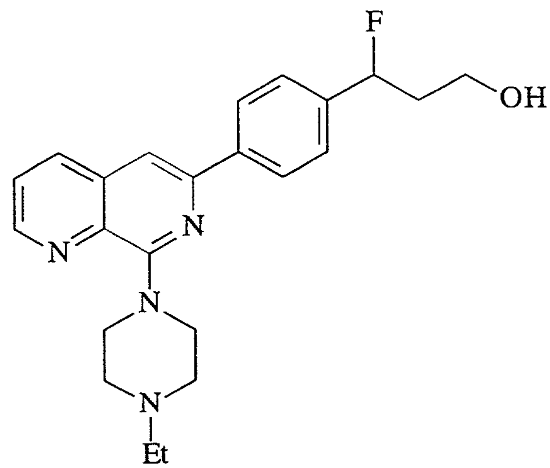
m.p.; 118-121°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.08(3H,d,J=6.4Hz), 1.29(3H,t,J=7.2Hz), 1.60-1.67(2H,m), 2.58-2.75(2H,m), 3.15(1H,q,J=7.2Hz), 3.17(1H,q,J=7.2Hz), 3.19(1H,t,J=10.8Hz), 3.22(1H,t,J=10.8Hz), 3.55-3.64(5H,m), 5.13(2H,d,J=13.6Hz), 7.31(2H,d,J=8.8Hz), 7.70(1H,dd,J=8.4Hz,4.4Hz), 7.88(1H,s), 8.07(2H,d,J=8.8Hz), 8.33(1H,dd,J=8.4Hz,1.6Hz),

8.83(1H,dd,J=4.4Hz,1.6Hz), 11.00-11.10(1H,br-s).

ESI-Mass; 391(MH^+).

Example 249 Synthesis of 8-(1-ethylpiperazin-4-yl)-6-[4-(3-hydroxy-1-fluoropropyl)phenyl]-1,7-naphthyridine dihydrochloride



In the same manner as in Example 27, the hydrochloride of the title compound was obtained as yellow hygroscopic crystals (135 mg, yield; 30%) from 6-bromo-8-(1-ethylpiperazin-4-yl)-1,7-naphthyridine (321 mg).

Hydrochloride:

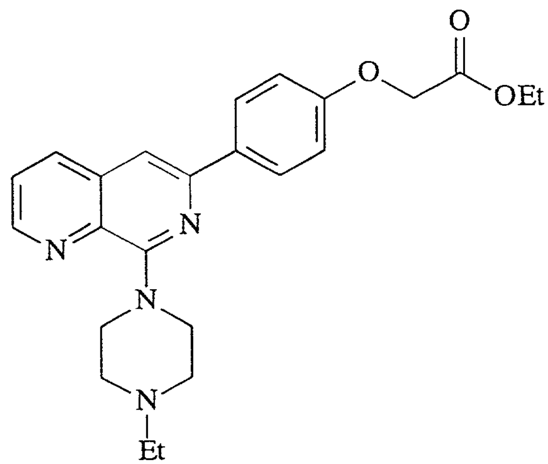
m.p.; 123-125°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.29(3H,t,J=7.2Hz), 1.70-2.20(2H,m), 3.13-3.27(4H,m), 3.45-3.65(5H,m), 5.15(2H,d,J=13.6Hz), 5.65(1H,ddd,J=48Hz,9.2Hz,4Hz), 7.50(2H,d,J=8.8Hz), 7.72(1H,dd,J=8.2Hz,4.4Hz), 7.96(1H,s), 8.20(2H,d,J=8.8Hz), 8.35(1H,dd,J=8.2Hz,1.6Hz), 8.86(1H,dd,J=4.4Hz,1.6Hz), 10.75-10.85(1H,br-s).

ESI-Mass; 395(MH^+).

Example 250 Synthesis of 8-(1-ethylpiperazin-4-yl)-6-[4-(2-hydroxy-2-methylpropoxy)phenyl]-1,7-naphthyridine dihydrochloride

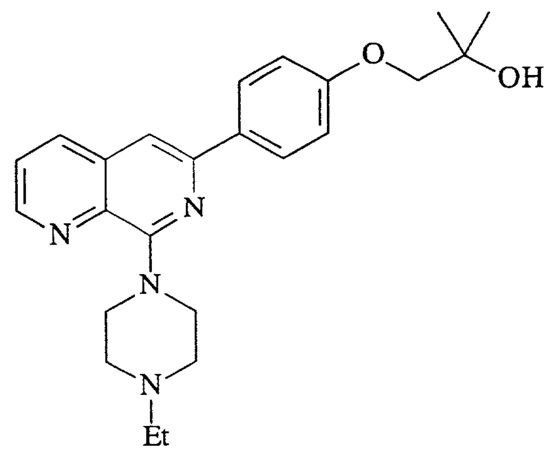
(250-1) 8-(1-Ethylpiperazin-4-yl)-6-[(4-ethoxycarbonylmethoxy)phenyl]-1,7-naphthyridine



In the same manner as in Example 161-3, the title compound was obtained as a yellow oil (362 mg, yield; 72%) from 6-bromo-8-(1-ethylpiperazin-4-yl)-1,7-naphthyridine (403 mg) and ethyl 2-(4-tributylstannylphenoxy)acetate (1.374 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(3H,t,J=7.2Hz), 1.32(3H,t,J=7.2Hz), 2.53(2H,q,J=7.2Hz), 2.74(4H,t,J=5Hz), 4.15(4H,t,J=5Hz), 4.29(2H,q,J=7.2Hz), 4.68(2H,s), 7.01(2H,d,J=8.8Hz), 7.42(1H,s), 7.44(1H,dd,J=8.4Hz,4Hz), 8.01(1H,dd,J=8.4Hz,1.6Hz), 8.75(1H,dd,J=4Hz,1.6Hz).

(250-2) 8-(1-Ethylpiperazin-4-yl)-6-[4-(2-hydroxy-2-methylpropoxy)phenyl]-1,7-naphthyridine dihydrochloride or compound identified by the following analysis data and synthetic procedure



In the same manner as in Example 260, the hydrochloride of the title compound was obtained as a yellow solid (348 mg, yield; 75%) from 8-(1-ethylpiperazin-4-yl)-6-[(4-ethoxycarbonylmethoxy)phenyl]-1,7-naphthyridine (362 mg) and a 3M solution of magnesium bromide/ether (1.5 ml).

Hydrochloride:

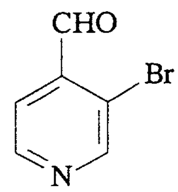
m.p.; 127-132°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.21(6H,s), 1.30(3H,t,J=7.2Hz), 3.15(1H,q,J=7.2Hz), 3.17(1H,q,J=7.2Hz), 3.18(1H,t,J=12Hz), 3.22(1H,t,J=12Hz), 3.60(2H,t,J=14.4Hz), 3.61(2H,d,J=12Hz), 3.77(2H,s), 5.10(2H,d,J=14.4Hz), 7.05(2H,d,J=8.8Hz), 7.68(1H,dd,J=8.4Hz,4Hz), 7.83(1H,s), 8.11(2H,d,J=8.8Hz), 8.30(1H,dd,J=8.4Hz,1.6Hz), 8.81(1H,dd,J=4Hz,1.6Hz), 11.05-11.15(1H,br-s).

ESI-Mass; 407(MH^+).

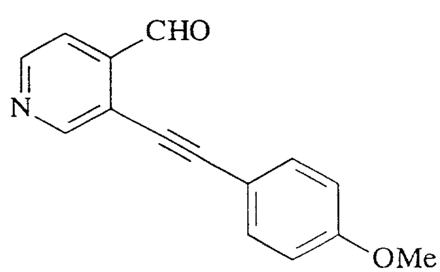
<u>Example 251 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(4-methoxyphenyl)-2,6-naphthyridine dihydrochloride</u>

<u>(251-1) 3-Bromo-4-pyridinecarboxaldehyde</u>



3-Bromopyridine (1.582 g) was dissolved in tetrahydrofuran (20 ml), followed by the addition of a 1.5M solution of lithium diisopropylamide/cyclohexane (7.3 ml) in nitrogen atmosphere at -70 °C, and the resulting mixture was stirred for 5 min. Continuously, 4-formylmorpholine (3 ml) was added thereto and stirried for 20 min, followed by the further stirring at room temperature for 30 min. An aqueous solution of saturated ammonium chloride was added to the reaction mixture, and then it was extracted with ethyl acetate. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a colorless solid (749 mg, yield; 40%).
^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 7.70(1H,d,J=4.6Hz), 8.91(1H,s), 10.36(1H,s).

<u>(251-2) 3-(4-Methoxyphenylethynyl)-4-pyridinecarboxaldehyde</u>

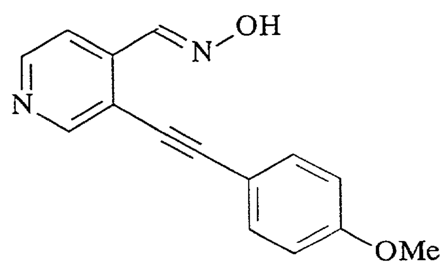


In the same manner as in Example 177, the title compound was obtained as a pale yellow solid (4.965 g, yield; 82%) from

3-bromo-4-pyridinecarboxyaldehyde (4.755 g) and 4-methoxyphenylacetylene (3.742 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 3.86(3H,s), 6.93(2H,d,J=8.8Hz), 7.70(1H,dd,J=5.2Hz,0.8Hz), 8.70(1H,dd,J=5.2Hz,0.8Hz), 8.94(1H,d,J=0.8Hz), 10.62(1H,s).

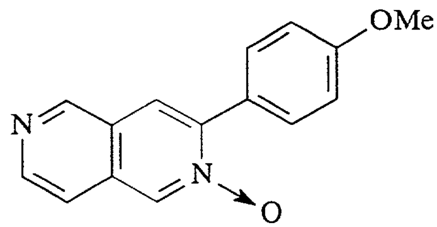
(251-3) 3-(4-Methoxyphenylethynyl)-4-pyridine aldoxime



3-(4-Methoxyphenylethynyl)-4-pyridinecarboxaldehyde (4.965 g) was dissolved in ethanol (70 ml), a solution of hydroxylamine hydrochloride (2.179 g) and sodium acetate (3.429 g) in water (18 ml) was added thereto, and then the mixture was stirred at 70°C overnight. After cooling as it was, the reaction mixture was evaporated and partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a yellow solid (4.724 g, yield; 96%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 3.85(3H,s), 6.92(2H,d,J=8.8Hz), 7.51(2H,d,J=8.8Hz), 7.73(1H,dd,J=5.2Hz,0.8Hz), 7.97(1H,s), 8.50(1H,dd,J=5.2Hz,0.8Hz), 8.62(1H,s), 8.78(1H,d,J=0.8Hz).

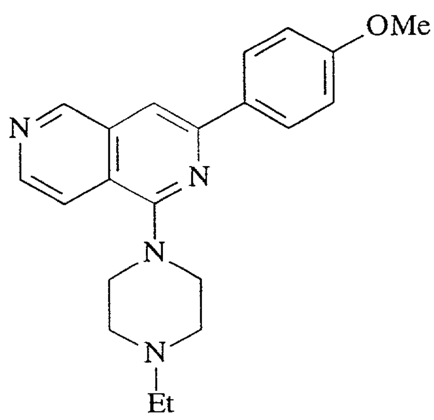
(251-4) 3-(4-Methoxyphenyl)-2,6-naphthyridine-2-oxide



3-(4-Methoxyphenylethynyl)-4-pyridine aldoxime (4.724 g) was dissolved in ethanol (100 ml), followed by the addition of potassium carbonate (2.768 g)/water (30 ml) solution, and the mixture was stirred at 70°C for 50 min. After cooling as it was, the resulting insoluble matters were collected by filtration, and then washed with water and ethanol, to give the title compound as a dark green solid (3.757 g, yield; 75%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 3.89(3H,s), 7.04(2H,d,J=8.8Hz), 7.50(1H,dd,J=6.2Hz,0.8Hz), 7.77(2H,d,J=8.8Hz), 7.88(1H,s), 8.61(1H,d,J=6.2Hz), 8.85(1H,s), 8.78(1H,d,J=0.8Hz).

<u>(251-5) 1-(1-Ethylpiperazin-4-yl)-3-(4-methoxyphenyl)-2,6-naphthyridine dihydrochloride</u>



3-(4-Methoxyphenyl)-2,6-naphthyridine-2-oxide (234 mg) was dissolved in phosphorus oxychloride (6 ml), and the resulting mixture was heated under stirring at 110°C for 20 min.

After cooling as it was, the reaction solution was evaporated. To the resulting residue was added 1-ethylpiperazine (20 ml), which was then heated under stirring at 160°C for 45 min. The reaction mixture was evaporated, and the resulting residue was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by (NH) silica gel column chromatography (ethyl acetate/hexane system), and then the resulting product was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/isopropyl ether, to give the hydrochloride of the title compound as yellow crystals (91 mg, yield; 22%).

Hydrochloride:

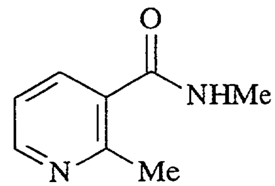
m.p.; 157-160°C

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.31(3H,t,J=7.2Hz), 3.19(1H,q,J=7.2Hz), 3.21(1H,q,J=7.2Hz), 3.29(1H,t,J=10.3Hz), 3.32(1H,t,J=10.3Hz), 3.59(2H,d,J=10.3Hz), 3.61(2H,t,J=12.8Hz), 4.09(2H,d,J=12.8Hz), 7.09(2H,d,J=8.8Hz), 8.10(1H,d,J=6Hz), 8.16(2H,d,J=8.8Hz), 8.19(1H,s), 8.61(1H,d,J=6Hz), 9.49(1H,s), 11.20(1H,br-s).

ESI-Mass; 349(MH^+).

Example 252 Synthesis of 5-(1-ethylpiperazin-4-yl)-7-(4-methoxyphenyl)-1,6-naphthyridine dihydrochloride

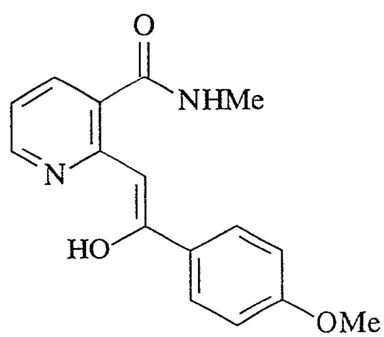
(252-1) 2-Methyl-N-methylnicotinamide



To ethyl 2-methylnicotinate (24.2 g) was added a solution of 40% methylamine in methanol (150 ml), which was then heated in a sealed tube at 50°C overnight. The reaction mixture was evaporated, to give the title compound as a pale yellow solid (20.781 g, yield; 95%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 3.27(3H,s), 4.08(3H,s), 7.48(1H,dd,J=7.8Hz,4.8Hz), 8.16(1H,dd,J=7.8Hz,1.6Hz), 8.87(1H,dd,J=4.8Hz,1.6Hz).

(252-2) 2-[2-(4-Methoxyphenyl)-2-hydroxyethenyl]-N-methylnicotinamide

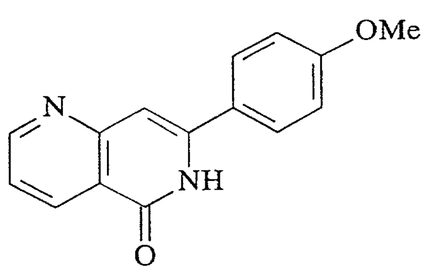


2-Methyl-N-methylnicotinamide (4.505 g) was dissolved in tetrahydrofuran (150 ml), followed by the dropwise addition of a solution of 1.5M lithium diisopropylamide in cyclohexane (40 ml) in nitrogen atmosphere at -30 to -20°C, and the mixture was stirred for 50 min. After cooling to -78°C, 4-methoxybenzonitrile (3.995 g)/tetrahydrofuran solution (20 ml) was added dropwise thereinto. After the mixture was stirred

for 1 hr as it was, the cooling bath was removed, and then it was stirred overnight. An aqueous solution of saturated ammonium chloride was added thereto, and then the mixture was extracted with ethyl acetate. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. A small amount of ethyl acetate was added to the resulting residue, and then the resulting insoluble matters were collected by filtration, to give 5.395 g of the title compound as a yellow solid.

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 2.75(3H,d,J=4.8Hz), 3.79(3H,s), 5.62(1H,s), 6.90(1H,dd,J=7.6Hz,4.8Hz), 7.01(2H,d,J=8.8Hz), 7.52(2H,d,J=8.8Hz), 7.53(1H,dd,J=7.6Hz,2Hz), 8.27(1H,q,J=4.8Hz), 8.42(1H,dd,J=4.8Hz,2Hz).

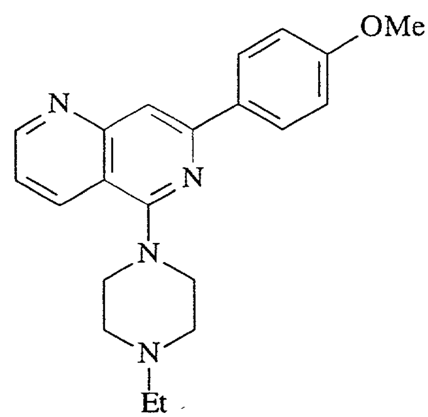
(252-3) 7-(4-Methoxyphenyl)-1,6-naphthyridin-5-(6H)-one



2-[2-(4-Methoxyphenyl)-2-hydroxyethenyl]-N-methylnicotinamide (2.509 g) was added to a 29% aqueous solution of ammonia (100 ml) and dioxane (50 ml), which was then heated in a sealed tube at 170°C overnight. After cooling as it was, the resulting insoluble matters were collected by filtration, to give the title compound as a dark green solid (1.694 g, yield; 73%).

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 3.83(3H,s), 6.87(1H,s), 7.07(2H,d,J=8.8Hz), 7.46(1H,dd,J=8Hz,4Hz), 7.81(2H,d,J=8.8Hz), 8.45(2H,d,J=8.8Hz), 8.45(1H,dd,J=8Hz,1.6Hz), 8.91(1H,dd,J=4.4Hz,1.6Hz).

(252-4) 5-(1-Ethylpiperazin-4-yl)-7-(4-methoxyphenyl)-1,6-naphthyridine dihydrochloride



Phosphorus oxychloride (10 ml) was added to 7-(4-methoxyphenyl)-1,6-naphthyridin-5-(6H)-one (1.505 g), and the resulting mixture was heated under stirring at 100°C for 6 hr. After cooling as it was, the reaction mixture was evaporated, followed by the addition of 1-ethylpiperazine (10 ml). The resulting mixture was heated under stirring at 150°C overnight, and then evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), and then the resulting product was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/isopropyl ether, to give the hydrochloride of the title compound as yellow crystals (1.974 g, yield; 78%).

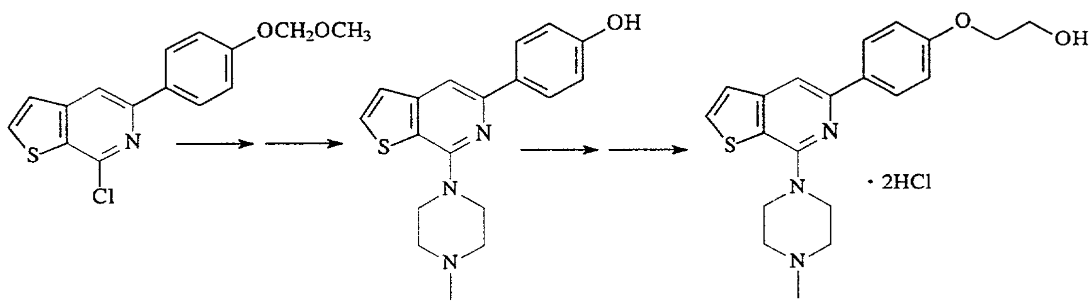
Hydrochloride:

m.p.; 242-245°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.30(3H,t,J=7.2Hz), 3.14-3.35(4H,m), 3.54-3.68(4H,m), 3.82(3H,s), 4.08(2H,d,J=14Hz), 7.08(2H,d,J=8.8Hz), 7.66(1H,dd,J=8.4Hz,4.2Hz), 8.00(1H,s), 8.17(2H,d,J=8.8Hz), 8.71(1H,dd,J=8.4Hz,1.6Hz), 9.09(1H,dd,J=4.2Hz,1.6Hz), 11.28(1H,br-s).

ESI-Mass; 349(MH$^+$).

Example 253 Synthesis of 5-[4-(2-hydroxyethoxy)phenyl]-7-(4-methylpiperazin-1-yl)thieno[2,3-c]pyridine hydrochloride



An oil (794 mg) was obtained from 7-chloro-5-(4-methoxymethoxyphenyl)thieno[2,3-c]pyridine (432 mg) obtained by the same treatment as in Example 18 and N-methylpiperazine (8 ml). To the resulting oil was added 5N hydrochloric acid/ethanol (6 ml), and the mixture was heated under reflux for 3 hr. The reaction solution was cooled and subsequently neutralized with a 5N aqueous solution of sodium hydroxide, and then extracted with chloroform. The resulting organic layer was washed with water, dried and evaporated, to give 5-(4-hydroxyphenyl)-7-(4-methylpiperazin-1-yl)thieno[2,3-c]pyridine (433 mg). To a solution of the resulting compound in dimethylformamide (6 ml) were added 60% sodium hydride (212

mg) and 2-bromoethoxy t-butyldimethylsilane (1.7 ml), and the mixture was reacted at 80°C for 3 hr. The reaction solution was poured into an aqueous solution of saturated ammonium chloride, and then extracted with ethyl acetate. The resulting organic layer was washed with water and brine, dried and evaporated. Sequentially, to the resulting residue were added tetrahydrofuran (10 ml) and 1.0M tetrabutylammonium fluoride/tetrahydrofuran solution (10 ml), and the mixture was stirred at room temperature for 30 min. The reaction solution was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and evaporated. The resulting residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate system), to give a yellow oil (210 mg, yield; 43%). The resulting oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 141-143°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 2.83(d,J=4.8Hz,3H), 3.14-3.29(m,2H), 3.49-3.58(m,4H), 3.75(t,J=4.8Hz,2H), 4.05(t,J=4.8Hz,2H), 4.40(d,J=14.0Hz,2H), 7.05(d,J=8.8Hz,2H), 7.54(d,J=5.6Hz,1H), 7.97(s,1H), 8.06(d,J=5.6Hz,1H), 8.08(d,J=8.8Hz,2H).

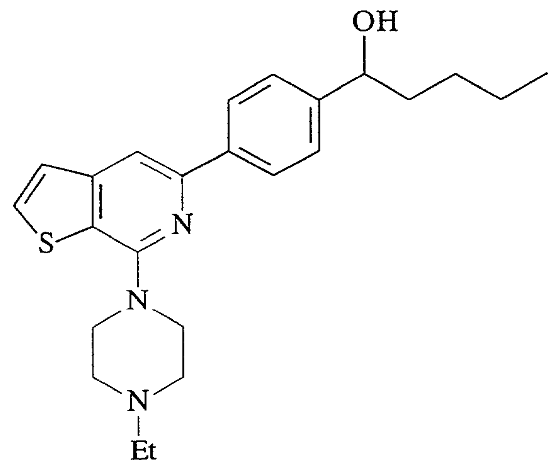
MS(FAB) m/z 370(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 2.39(s,3H), 2.65(t,J=4.8Hz,4H),

3.83(t,J=4.8Hz,4H), 3.99(t,J=4.4Hz,2H), 4.15(t,J=4.4Hz,2H), 7.00(d,J=8.8Hz,2H), 7.33(d,J=5.6Hz,1H), 7.55(d,J=5.6Hz,1H), 7.62(s,1H), 8.05(d,J=8.8Hz,2H).

Example 254 Synthesis of 7-(1-ethylpiperazin-4-yl)-5-[4-(1-hydroxypentyl)phenyl]thieno[2,3-c]pyridine dihydrochloride



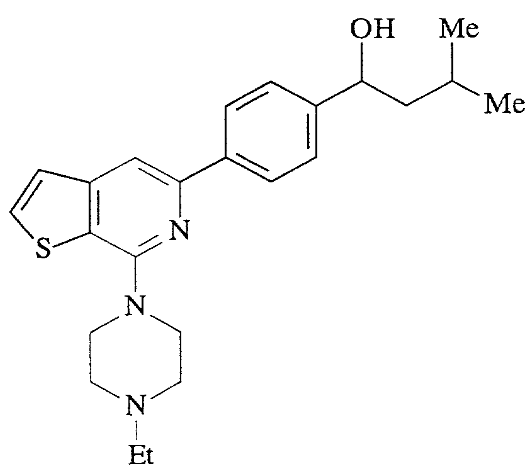
7-(1-Ethylpiperazin-4-yl)-5-(4-pentanoylphenyl)thieno[2,3-c]pyridine (206 mg) was dissolved in tetrahydrofuran (12 ml), followed by the addition of lithium aluminum hydride (20 mg) under ice-cooling, and the mixture was stirred for 15 min. To the reaction mixture were sequentially added water (20 ml), 5N sodium hydroxide (20 ml) and water (60 ml). The resulting insoluble matters were filtered off through Celite, and then the resulting filtrate was evaporated. The resulting residue was purified by (NH) silica gel column chromatography (ethyl acetate/hexane system). The resulting product was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as a yellow amorphous (196 mg, yield; 80%).

Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.83(3H,t,J=7Hz), 1.08-1.30(4H,m), 1.29(3H,t,J=7.2Hz), 1.52-1.68(2H,m), 3.12-3.22(4H,m), 3.54-3.63(4H,m), 4.40(2H,d,J=14Hz), 4.54(1H,t,J=6.4Hz), 7.40(2H,d,J=8Hz), 7.55(1H,d,J=5.4Hz), 8.00(1H,s), 8.05(2H,d,J=8Hz), 8.06(1H,d,J=5.4Hz), 11.10-11.20(1H,br-s).

ESI-Mass; 410(MH^+).

Example 255 Synthesis of 7-(1-ethylpiperazin-4-yl)-5-[4-(1-hydroxy-3-methylbutyl)phenyl]thieno[2,3-c]pyridine dihydrochloride



In the same manner as in Example 254, the hydrochloride of the titled compound was obtained as a yellow amorphous (149 mg, yield; 60%) from 7-(1-ethylpiperazin-4-yl)-5-(4-isopentanoylphenyl)thieno[2,3-c]pyridine (212 mg).

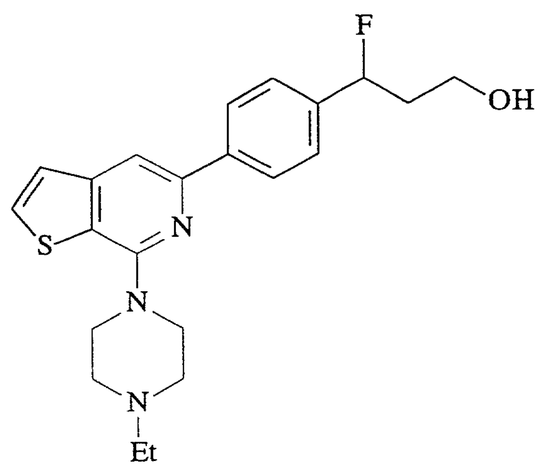
Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.89(3H,d,J=6.4Hz), 0.90(3H,d,J=6.4Hz), 1.29(3H,t,J=7.2Hz), 1.32-1.40(1H,m),

1.53-1.70(2H,m), 3.13-3.22(4H,m), 3.54-3.63(4H,m), 4.40(2H,d,J=14Hz), 4.60(1H,dd,J=8.6Hz,5Hz), 7.41(2H,d,J=8.4Hz), 7.55(1H,d,J=5.4Hz), 8.00(1H,s), 8.05(2H,d,J=8.4Hz), 8.06(1H,d,J=5.4Hz), 11.10-11.20(1H,br-s).

ESI-Mass; 410(MH^+).

Example 256 Synthesis of 7-(1-ethylpiperazin-4-yl)-5-[4-(3-hydroxy-1-fluoropropyl)phenyl]thieno[2,3-c]pyridine dihydrochloride



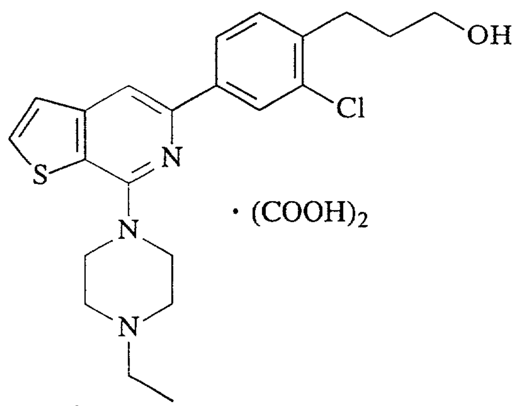
In the same manner as in Example 27, the hydrochloride of the title compound was obtained as a hygroscopic yellow amorphous (101 mg, yield; 20%) from 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (330 mg).

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.29(3H,t,J=7.2Hz), 1.65-2.20(2H,m), 3.10-3.24(4H,m), 3.30-3.65(6H,m), 4.42(2H,d,J=13.6Hz), 5.70(1H,ddd,J=48Hz,9.2Hz,4Hz), 7.48(2H,d,J=8.8Hz), 7.56(1H,d,J=5.6Hz), 8.05(1H,s), 8.08(1H,d,J=5.6Hz), 8.15(2H,d,J=8.8Hz), 11.05-11.15(1H,br-

s).

ESI-Mass; 400(MH^+).

Example 257 Synthesis of 5-[4-(3-hydroxypropyl)-3-chlorophenyl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine oxalate



In the same manners sequentially as in Examples 161-2 and 20, an oil was obtained from 1-bromo-4-(3-acetoxypropyl)-3-chlorobenzene (948 mg) and 5-bromo-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine (243 mg). To the resulting oil were added tetrahydrofuran (10 ml) and 1.0 M lithium aluminum hydride/tetrahydrofuran solution (0.8 ml) under ice-cooling, and the mixture was reacted under ice-cooling for 1 hr. Subsequently, water (0.03 ml), a 5N aqueous solution of sodium hydroxide (0.03 ml) and water (0.09 ml) were sequentially added to the resulting mixture, and then the mixture was stirred at room temperature for 1 hr. The resulting residue was filtered, washed with ethyl acetate, and then purified by silica gel column chromatography (hexane/ethyl acetate system), to give a colorless oil. The resulting oil was converted into an

oxalate in a conventional manner, to give the oxalate of the title compound as white crystals (205 mg, yield; 60%).

Oxalate:

m.p.; 114-116°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.22(t,J=7.2Hz,3H), 1.76(t,J=7.6Hz,2H), 2.78(t,J=7.6Hz,2H), 2.99(q,J=7.2Hz,2H), 3.20(br,4H), 3.48(t,J=7.6Hz,2H), 3.89(br,4H), 7.44(d,J=8.0Hz,1H), 7.55(d,J=5.2Hz,1H), 8.02(d,J=8.0Hz,1H), 8.05(s,1H), 8.08(d,J=5.2Hz,1H), 8.14(s,1H).

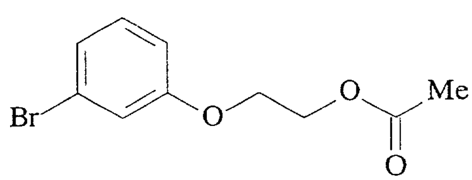
MS(FAB) m/z 416(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 1.91-1.98(m,2H), 2.52(q,J=7.2Hz,2H), 2.69(t,J=4.8Hz,4H), 2.88(t,J=7.6Hz,2H), 3.73(t,J=7.6Hz,2H), 3.85(t,J=4.8Hz,4H), 7.31(d,J=8.0Hz,1H), 7.34(d,J=5.6Hz,1H), 7.58(d,J=5.6Hz,1H), 7.64(s,1H), 7.90(dd,J=8.0,2.0Hz,1H), 8.09(d,J=2.0Hz,1H).

Example 258 Synthesis of 7-(1-ethylpiperazin-4-yl)-5-[3-(2-hydroxyethoxy)phenyl]thieno[2,3-c]pyridine dihydrochloride

(258-1) 3-Bromophenoxyethyl acetate

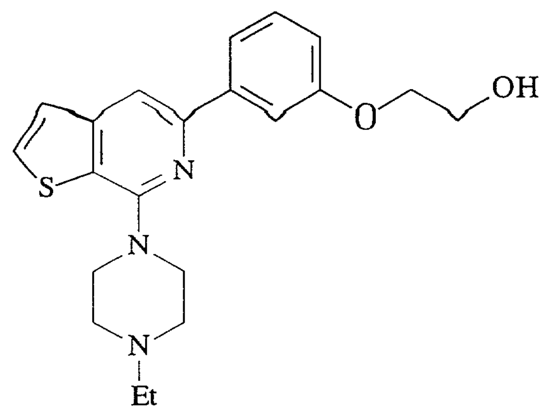


In the same manner as in Example 300-2, the titled compound was obtained as a colorless oil (11.213 g, yield; 74%) from 3-bromophenol (10.062 g) and 2-bromoethyl acetate (24.4 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 2.10(3H,s), 4.15(2H,t,J=4.6Hz),

4.41(2H,t,J=4.6Hz), 6.85(1H,ddd,J=8Hz,2.4Hz,1.2Hz), 7.07-7.12(2H,m), 7.15(1H,t,J=8Hz).

(258-2) 7-(1-Ethylpiperazin-4-yl)-5-[3-(2-hydroxyethoxy)phenyl]thieno[2,3-c]pyridine dihydrochloride



In the same manner as in Example 161-1, 3-tributylstannylphenoxyethyl acetate of was obtained as a colorless oil (2.255 g) from 3-bromophenoxyethyl acetate (3.454 g) and bis(tributyltin) (5.1 ml). A part (394 mg) of the resulting compound and 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (137 mg) were treated in the same manner as in Example 300-4, to give the hydrochloride of the title compound as pale yellow crystals (34 mg, yield; 18%).

Hydrochloride:

m.p.; 132-135°C

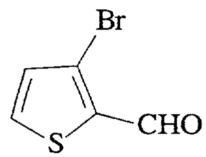
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.29(3H,t,J=7.2Hz), 3.13-3.22(4H,m), 3.58(2H,t,J=14.4Hz), 3.62(2H,d,J=11.2Hz), 3.74(2H,t,J=5.2Hz), 4.07(2H,t,J=5.2Hz), 4.40(2H,d,J=14.4Hz), 6.97(1H,ddd,J=8Hz,2.6Hz,1.6Hz), 7.37(1H,t,J=8Hz), 7.55(1H,d,J=5.6Hz), 7.68(1H,dd,J=2.6Hz,1Hz),

7.69(1H,ddd,J=8Hz,1.6Hz,1Hz), 8.05(1H,s), 8.06(1H,d,J=5.6Hz), 11.15-11.25(1H,br-s).

FAB-Mass; 384(MH^+).

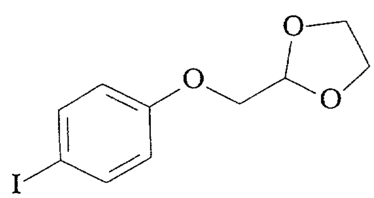
Example 259 Synthesis of 7-(4-ethylpiperazin-1-yl)-5-(4-hydroxyethoxyphenyl)thieno[2,3-c]pyridine hydrochloride

(259-1) 3-Bromo-2-thiophenecarboxaldehyde



Methyl 3-amino-2-thiophenecarboxylate (23.5 g) was converted into methyl 3-bromo-2-thiophenecarboxylate (20.8 g) by Sandmeyer's method, and the resulting ester was reduced with lithium aluminum hydride (2.8 g). Continuously, the resulting compound was oxidized with activated manganese dioxide (30.0 g), to give 14.5 g of the title compound.

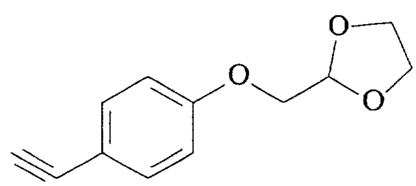
(259-2) 1-[(1,3-Dioxolan-2-yl)methyloxy]-4-iodobenzene



A suspension of 65% sodium hydride (9.3 g)/dimethylformamide (100 ml) was ice-cooled, followed by the addition of 4-iodophenol (50.5 g)/dimethylformamide (200 ml) solution, and the mixture was stirred for 3 hr. To the mixture solution was added (1,3-dioxolan-2-yl)methyl bromide (46.0 g), and the mixture was reacted at 60°C for 1 day. The reaction

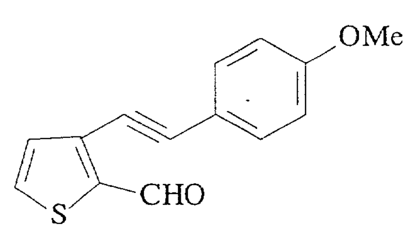
solution was poured into water, and extracted with ethyl acetate. The resulting organic layer was washed with water and brine, and then dried (over magnesium sulfate). The solvent was removed, and the resulting residue was purified by NH silica gel column chromatography (chloroform), and then recrystallized from ethyl acetate/hexane, to give 32.7 g of the title compound as pale yellow prisms.

(259-3) 1-[(1,3-Dioxolan-2-yl)methyloxy]-4-ethynylbenzene



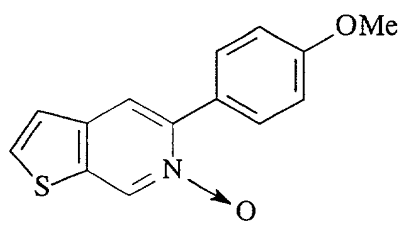
1-[(1,3-Dioxolan-2-yl)methyloxy]-4-iodobenzene (36.3 g) and trimethylsilylacetylene (50.0 g) were reacted in the presence of bistriphenylphosphinepalladium dichloride (2.50 g) and cuprous iodide (1.25 g), in triethylamine (140 ml) and pyridine (70 ml) at 60°C for 2 hr. The reaction solution was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and concentrated. The resulting residue was dissolved in methanol and treated with 2N sodium hydroxide, to give 20.1 g of the title compound.

(259-4) 3-[2-(4-Methoxyphenyl)ethynyl]-2-thiophenecarboxyaldehyde



3-Bromo-2-thiophenecarboxyaldehyde (7.5 g) and 1-[(1,3-dioxolan-2-yl)methyloxy]-4-ethynylbenzene (7.8 g) were reacted in dimethylformamide (25 ml), in the presence of bistriphenylphosphinepalladium dichloride (0.48 g), cuprous iodide (0.13 g) and triethylamine (25 ml) at 60°C for 12 hr. The reaction solution was evaporated, extracted with ethyl acetate, washed with water and dried. The solvent was removed, and the resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give 7.2 g of the title compound as a pale yellow oil.

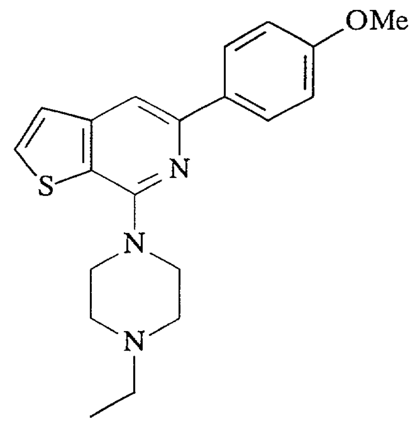
(259-5) 5-(4-Methoxyphenyl)thieno[2,3-c]pyridine-6-oxide



3-[2-(4-Methoxyphenyl)ethynyl]-2-thiophenecarboxyaldehyde (7.2 g), hydroxylamine hydrochloride (2.4 g) and sodium acetate (3.3 g) were reacted in ethanol (100 ml) at 60°C for 2 hr. Then the resulting solution was concentrated. Potassium carbonate (3.0 g), water (10 ml) and 1-butanol (50 ml) were added to the resulting residue, and the mixture was reacted at 100°C for 3 days. The reaction solution was evaporated, extracted with methylene chloride, washed with brine and dried. The solvent was removed, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 3.04 g of the

title compound as a white amorphous.

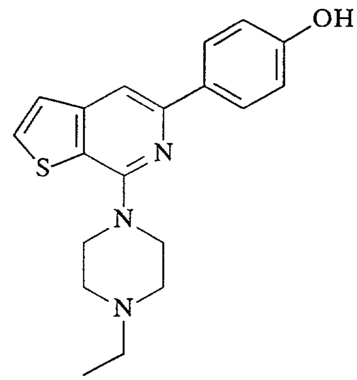
(259-6) 7-(4-Ethylpiperazin-1-yl)-5-(4-methoxyphenyl)thieno[2,3-c]pyridine



5-(4-Methoxyphenyl)thieno[2,3-c]pyridine-6-oxide (3.0 g) was reacted with phosphorus oxychloride (15 ml) at 100°C for 3 hr. The reaction mixture was poured into ice-water, neutralized with sodium carbonate and extracted with ethyl acetate. The organic layer was washed with water and brine and dried. The extract was filtered through silica gel, and the column was washed with ethyl acetate. The filtrates were combined and concentrated. The resulting 7-chloro-5-(4-methoxyphenyl)thieno[2,3-c]pyridine (2.1 g) was reacted reacted in N-ethylpiperazine (5 ml) and dimethyl sulfoxide (20 ml) with potassium carbonate (5.0 g) at 100°C for 1 day. The reaction solution was evaporated, and the resulting residue was partitioned between ethyl acetate and water and extracted with ethyl acetate. The organic layer was washed with water and dried. Then, the solvent was removed, and the resulting residue was purified by silica gel column chromatography (methylene

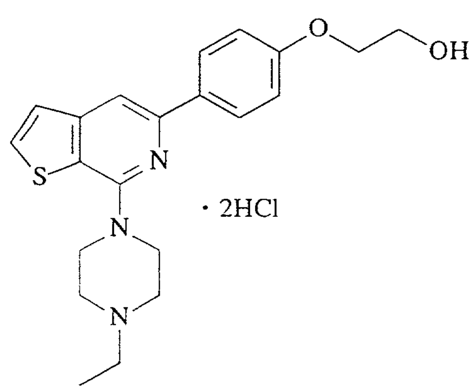
chloride/methanol system), to give 0.93 g of the title compound of as a pale brown oil.

(259-7) 7-(4-Ethylpiperazin-4-yl)-5-(4-hydroxyphenyl)thieno[2,3-c]pyridine



7-(4-Ethylpiperazin-1-yl)-5-(4-methoxyphenyl)thieno[2,3-c]pyridine (0.43 g) was reacted with 48% hydrobromic acid (10 ml) at 120°C for 2 hr. The reaction solution was cooled, and then neutralized with 5N sodium hydroxide and extracted with chloroform. The resulting organic layer was washed with water, dried and concentrated. The resulting pale brown solid was washed with hexane/ethyl acetate (20:1), to give 0.13 g of the title compound.

(259-8) 7-(4-Ethylpiperazin-1-yl)-5-[4-(2-hydroxyethoxy)phenyl]thieno[2,3-c]pyridine



To 7-(4-ethylpiperazin-1-yl)-5-(4-hydroxyphenyl)thieno[2,3-c]pyridine (130 mg)/dimethylformamide (10 ml) solution was added 60% sodium hydride (23 mg) at room temperature. After the evolution of hydrogen was ceased, dimethyl-(t-butyl)silyloxyethyl bromide (100 mg) was added thereto, and the mixture was reacted at room temperature for 12 hr. Ethyl acetate and an aqueous solution of ammonium chloride were added to the reaction solution. The organic phase was separated, washed with water, dried and concentrated. To the resulting residue were added ethanol (20 ml) and a 2N aqueous solution of hydrochloric acid (10 ml), and the mixture was reacted at 50°C for 30 min, followed by the evaporation. The resulting residue was partitioned between ethyl acetate and water. The organic layer was washed with water and brine, and dried. The solvent was removed, and the resulting residue was purified by NH-silica gel column chromatography (ethyl acetate), to give 73 mg of the title compound as a pale yellow oil.

The resulting compound was converted into a hydrochloride in a conventional manner, to give 77mg of the title compound as a yellow powder.

Hydrochloride:

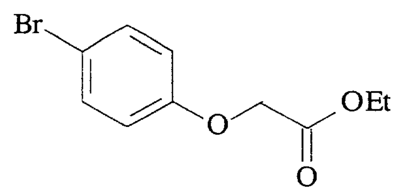
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.28(t,J=7.2Hz,3H), 3.14-3.25(m,4H), 3.54(br-t,2H), 3.63(br-d,2H), 3.73(m,2H), 3.90-4.18(m,2H), 4.41(br-d,2H), 7.03(d,J=8.4Hz,2H), 7.54(d,J=5.6Hz,1H), 7.97(s,1H), 8.03-8.10(m,2H).

m.p.; 135-136°C

MS(FAB) m/z 384(M+H)$^+$.

Example 260 Synthesis of 7-(1-ethylpiperazin-4-yl)-5-[4-(2-hydroxy-2-methylpropoxy)phenyl]thieno[2,3-c]pyridine dihydrochloride

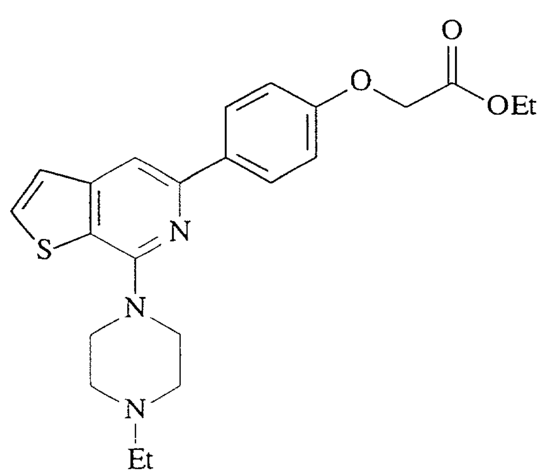
(260-1) Ethyl (4-bromophenoxy)acetate



In the same manner as in Example 300-2, the titled compound was obtained as a colorless solid (41.938 g, yield; 92%) from 2-bromophenol (30.121 g) and ethyl bromoacetate (40.304 g).

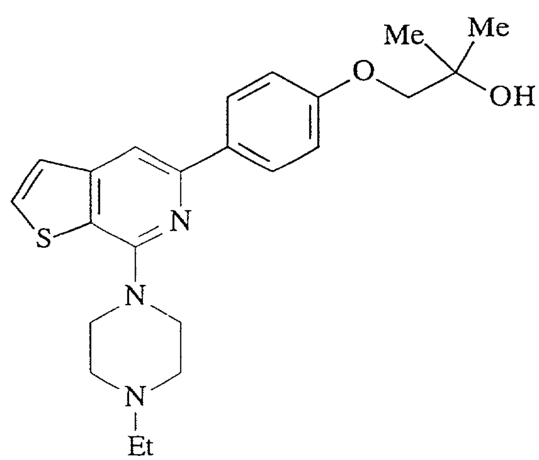
^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.30(3H,t,J=7.2Hz), 4.27(2H,q,J=7.2Hz), 4.59(2H,s), 6.80(2H,d,J=8.8Hz), 7.39(2H,d,J=8.8Hz).

(260-2) 7-(1-Ethylpiperazin-4-yl)-5-[(4-ethoxycarbonylmethoxy)phenyl]thieno[2,3-c]pyridine



In the same manner as in Example 161-2, ethyl (4-tributylstannylphenoxy)acetate was obtained as a colorless oil (5.594 g) from ethyl (4-bromophenoxy)acetate (9.069 g) and bis(tributyltin) (18 ml). The resulting compound and 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (368 mg) were treated in the same manner as in Example 161-3, to give the title compound as a colorless oil (339 mg, yield; 73%).
^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(3H,t,J=7.2Hz), 1.31(3H,t,J=7.2Hz), 2.51(2H,q,J=7.2Hz), 2.68(4H,t,J=5Hz), 3.84(4H,t,J=5Hz), 4.29(2H,q,J=7.2Hz), 4.70(2H,s), 6.99(2H,d,J=8.8Hz), 7.32(1H,d,J=5.2Hz), 7.54(1H,d,J=5.2Hz), 7.60(1H,s), 8.05(2H,d,J=8.8Hz).

(260-3) 7-(1-Ethylpiperazin-4-yl)-5-[4-(2-hydroxy-2-methylpropoxy)phenyl]thieno[2,3-c]pyridine dihydrochloride or compound identified by the following analysis data and synthetic procedures



7-(1-Ethylpiperazin-4-yl)-5-[(4-ethoxycarbonylmethoxy)phenyl]thieno[2,3-c]pyridine (339 mg)

was dissolved in tetrahydrofuran (12 ml), followed by the addition of 3M methylmagnesium bromide/ether solution (1.3 ml) under ice-cooling, and the mixture was stirred for 1 hr. An aqueous saturated ammonium chloride was added to the reaction mixture, and then extracted with ethyl acetate. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by (NH) silica gel column chromatography (ethyl acetate/hexane system). Then, the resulting product was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/isopropyl ether, to give the hydrochloride of the title compound as a pale yellow solid (326 mg, yield; 88%).

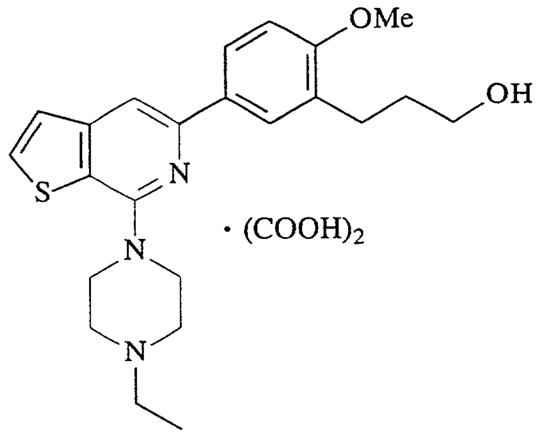
Hydrochloride:

m.p.; 137-139°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.21(6H.s), 1.29(3H,t,J=7.2Hz), 3.13-3.23(4H,m), 3.53(2H,t,J=13.6Hz), 3.63(2H,d,J=11.6Hz), 3.76(2H,s), 4.39(2H,d,J=13.6Hz), 7.03(2H,d,J=8.8Hz), 7.52(1H,d,J=5.6Hz), 7.95(1H,s), 8.04(1H,d,J=5.6Hz), 8.06(2H,d,J=8.8Hz), 10.90(1H,br-s).

FAB-Mass; 412(MH^+).

Example 261 Synthesis of 5-[3-(3-hydroxypropyl)-4-methoxyphenyl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine oxalate



In the same manners sequentially as in Examples 161-2 and 20, an oil was obtained prepared from 1-bromo-3-(3-acetoxypropyl)-4-methoxybenzene (2.57 g) and 5-bromo-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine (1.7 g). To the resulting oil were added methanol (9 ml) and a 1N aqueous solution of sodium hydroxide (1 ml), and the mixture was heated under reflux for 1 hr. The reaction solution was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system), to give a colorless oil (188 mg, yield; 64%). The resulting oil was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 98-102°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.21(t,J=7.2Hz,3H), 1.65-1.78(m,4H), 2.66(t,J=7.2Hz,2H), 2.97(q,J=7.2Hz,2H), 3.72(br,4H), 3.46(t,J=6.8Hz,2H), 3.59-3.62(m,2H), 3.84(s,3H),

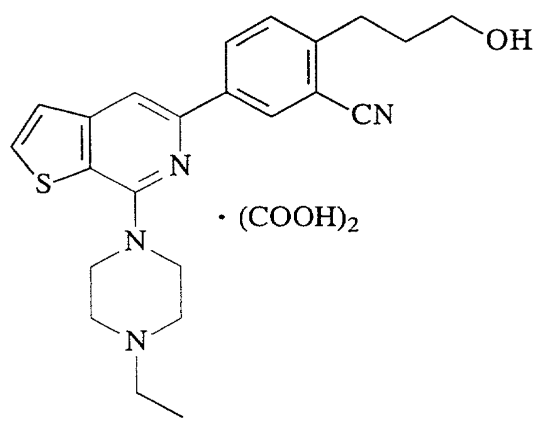
7.05(d,J=8.4Hz,1H), 7.53(d,J=5.2Hz,1H), 7.89(br,1H), 7.92(s,1H), 7.96(d,J=8.4Hz,1H), 8.03(d,J=5.2Hz,1H).

MS(FAB) m/z 412$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.6Hz,3H), 1.88-1.94(m,2H), 2.51(q,J=7.6Hz,2H), 2.69(t,J=4.8Hz,4H), 2.81(t,J=7.2Hz,2H), 3.65(t,J=6.0Hz,2H), 3.84(t,J=4.8Hz,4H), 3.88(s,3H), 6.94(d,J=8.8Hz,1H), 7.32(d,J=5.6Hz,1H), 7.54(d,J=5.6Hz,1H), 7.61(s,1H), 7.87(d,J=2.4Hz,1H), 7.94(dd,J=8.8,2.0Hz,1H).

Example 262 Synthesis of 5-[4-(3-hydroxypropyl)-3-cyanophenyl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine oxalate



In the same manners sequentially as in Examples 161-2 and 20, a yellow oil was obtained from 1-bromo-4-(3-acetoxypropyl)-3-cyanobenzene (610 mg) and 5-bromo-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine (164 mg). To the resulting oil were added THF (5 ml), carbon tetrachloride (5 ml) and triphenylphosphine (630 mg), and the mixture was reacted

at 60°C for 2 hr. The reaction solution was partitioned between ethyl acetate and water, and the resulting organic layer was extracted with 2N hydrochloric acid. The aqueous layer was basified with 2N sodium hydroxide, and then back-extracted with ethyl acetate. The resulting organic layer was washed with water, dried and evaporated. To the resulting residue were added methanol (10 ml) and a 1N aqueous solution of sodium hydroxide (1 ml), and the mixture was reacted at 50°C for 30 min. The reaction solution was partitioned between ethyl acetate and water. The resulting organic layer was washed with brine, dried and evaporated. The resulting residue was purified by NH-silica gel column chromatography (ethyl acetate/hexane system), to give a yellow oil (75 mg, yield; 38%). The resulting oil was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 132-134°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.23(t,J=7.2Hz,3H), 1.76-1.84(m,2H), 2.88(t,J=7.6Hz,2H), 3.06(q,J=7.2Hz,2H), 3.27(br,4H), 3.48(t,J=5.2Hz,2H), 3.92(br,4H), 7.56(d,J=5.6Hz,1H), 7.60(d,J=8.4Hz,1H), 8.10(d,J=5.6Hz,1H), 8.13(s,1H), 8.38(dd,J=8.4,1.6Hz,1H), 8.49(d,J=1.6Hz,1H).

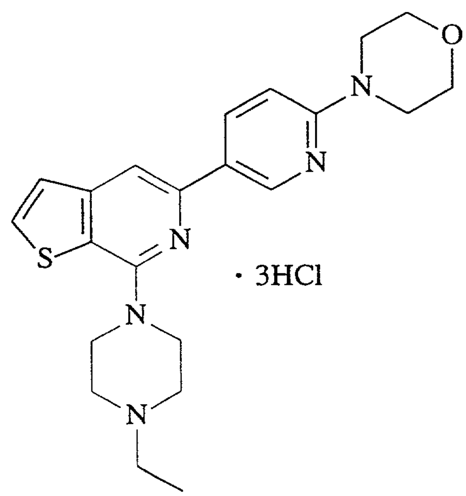
MS(FAB) m/z 407(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.6Hz,3H), 1.95-

2.05(m,2H), 2.53(q,J=7.6Hz,2H), 2.70(t,J=4.8Hz,4H), 3.00(t,J=7.6Hz,2H), 3.75(t,J=6.4Hz,2H), 3.87(t,J=4.8Hz,4H), 7.37(d,J=5.6Hz,1H), 7.43(d,J=8.0Hz,1H), 7.61(d,J=5.6Hz,1H), 7.65(s,1H), 8.22(dd,J=8.0,2.0Hz,1H), 8.37(d,J=2.0Hz,1H).

Example 263 Synthesis of 5-[2-(4-morpholinyl)pyridin-5-yl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, an oil was obtained (209 mg, yield; 83%) from 5-bromo-2-(4-morpholinyl)pyridine (756 mg) and 5-bromo-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine (200 mg). The resulting oil was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 182-185°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.32(t,J=7.2Hz,3H), 3.15-3.27(m,4H), 3.58-3.66(m,4H), 3.76-3.79(m,8H),

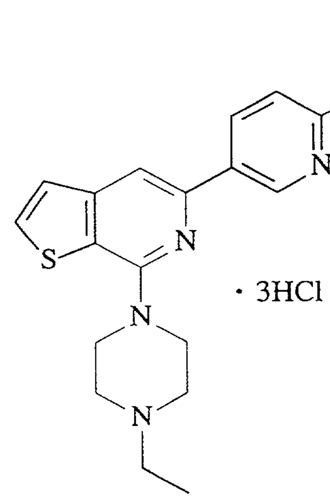
4.44(d,J=14.0Hz,2H), 7.45(d,J=9.6Hz,1H), 7.56(d,J=5.6Hz,1H), 8.11(s,1H), 8.13(d,J=5.6Hz,1H), 8.67(d,J=9.6Hz,1H), 8.69(s,1H).

MS(FAB) m/z 410$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.6Hz,3H), 2.51(q,J=7.6Hz,2H), 2.68(t,J=5.2Hz,4H), 3.58(t,J=5.2Hz,4H), 3.85(t,J=5.2Hz,8H), 6.72(d,J=8.8Hz,1H), 7.33(d,J=5.6Hz,1H), 7.56(d,J=5.6Hz,1H), 7.57(s,1H), 8.21(dd,J=8.8,2.4Hz,1H), 8.97(d,J=2.4Hz,1H).

Example 264 Synthesis of 5-[2-(4-thiomorpholinyl)pyridin-5-yl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, a colorless oil was obtained (240 mg, yield; 92%) from 5-bromo-2-(4-thiomorpholinyl)pyridine (848 mg) and 5-bromo-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine (200 mg). The resulting oil was converted into a hydrochloride in a

conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 201-203°C

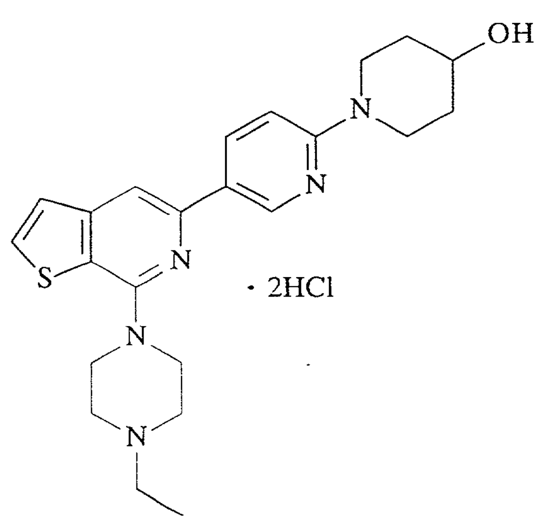
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.31(t,J=7.2Hz,3H), 2.75(br,4H), 3.16-3.26(m,4H), 3.55-3.66(m,4H), 4.10(br,4H), 4.42(d,J=14.0Hz,2H), 7.36(br,1H), 7.56(d,J=5.6Hz,1H), 8.07(s,1H), 8.11(d,J=5.6Hz,1H), 8.54(br,1H), 8.73(s,1H).

MS(FAB) m/z 426(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.6Hz,3H), 2.53(q,J=7.6Hz,2H), 2.66-2.72(m,4H), 2.69(t,J=4.8Hz,4H), 3.84(t,J=4.8Hz,4H), 4.02-4.04(m,4H), 6.70(d,J=8.8Hz,1H), 7.32(d,J=5.6Hz,1H), 7.55(d,J=5.6Hz,1H), 7.55(s,1H), 8.18(dd,J=8.8,2.4Hz,1H), 8.95(d,J=2.4Hz,1H).

Example 265 Synthesis of 5-[2-(4-hydroxypiperidin-1-yl)pyridin-5-yl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, an oil was obtained from 5-bromo-2-(4-hydroxypiperidin-1-yl)pyridine (554 mg) and 5-bromo-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine (200 mg). To the resulting oil were added methanol (10 ml) and a 1N aqueous solution of sodium hydroxide (1 ml), and the mixture was heated under reflux for 1 hr. The reaction solution was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system), to give a colorless oil (224 mg, yield; 86%). The resulting oil was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 208-210°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.25(t,J=7.2Hz,3H), 1.36-1.42(m,2H), 1.76-1.82(m,2H), 3.11-3.19(m,4H), 3.34(br,4H), 3.70-3.78(m,1H), 3.92(br,4H), 4.09(d,J=13.6Hz,2H), 6.93(d,J=8.8Hz,1H), 7.51(d,J=5.2Hz,1H), 7.90(s,1H), 8.04(d,J=5.2Hz,1H), 8.20(d,J=8.8Hz,1H), 8.89(s,1H).

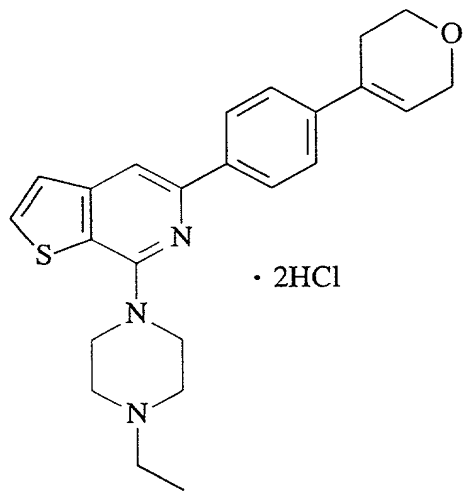
MS(FAB) m/z 424(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 1.58-1.64(m,2H), 1.99-2.05(m,2H), 2.51(q,J=7.2Hz,2H), 2.68(t,J=4.8Hz,4H), 3.24(dt,J=9.6,3.2Hz,2H),

3.85(t,J=4.8Hz,4H), 3.92-3.95(m,1H), 4.12-4.18(m,2H), 6.76(d,J=8.8Hz,1H), 7.32(d,J=5.6Hz,1H), 7.55(d,J=5.6Hz,1H), 7.55(s,1H), 8.18(dd,J=8.8,2.4Hz,1H), 8.95(d,J=2.4Hz,1H).

Example 266 Synthesis of 5-[4-(5,6-dihydro-2H-pyran-4-yl)phenyl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, a colorless oil was obtained (222 mg, yield; 89%) from 1-bromo-4-(5,6-dihydro-2H-pyran-4-yl)benzene (690 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (200 mg). The resulting oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 176-179°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.31(t,J=7.2Hz,3H), 3.20(br,4H), 3.57-3.70(m,4H), 3.85(t,J=5.2Hz,4H), 4.26(br,2H), 4.42(d,J=13.2Hz,2H), 6.37(s,1H),

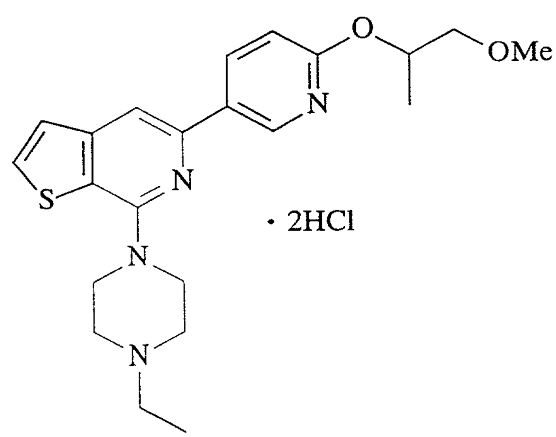
7.56(d,J=8.4Hz,2H), 7.57(d,J=5.6Hz,1H), 8.06(s,1H), 8.09(d,J=5.6Hz,1H), 8.13(d,J=8.4Hz,2H).

MS(FAB) m/z 406$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.6Hz,3H), 2.52(q,J=7.6Hz,2H), 2.57-2.59(m,2H), 2.69(t,J=5.2Hz,4H), 3.86(t,J=5.2Hz,4H), 3.97(t,J=5.6Hz,2H), 4.36(q,J=2.8Hz,2H), 6.21(br,1H), 7.35(d,J=5.6Hz,1H), 7.49(d,J=8.4Hz,2H), 7.57(d,J=5.6Hz,1H), 7.69(s,1H), 8.08(d,J=8.4Hz,2H).

<u>Example 267</u> <u>Synthesis of 5-[2-(2-methoxyethoxy-2-methyl)pyridin-5-yl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine hydrochloride</u>



In the same manners sequentially as in Examples 161-2 and 20, a colorless oil was obtained (193 mg, yield; 85%) from 5-bromo-2-(2-methoxyethoxy-2-methyl)pyridine (563 mg) and 5-bromo-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine (180 mg). The resulting oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 112-114°C

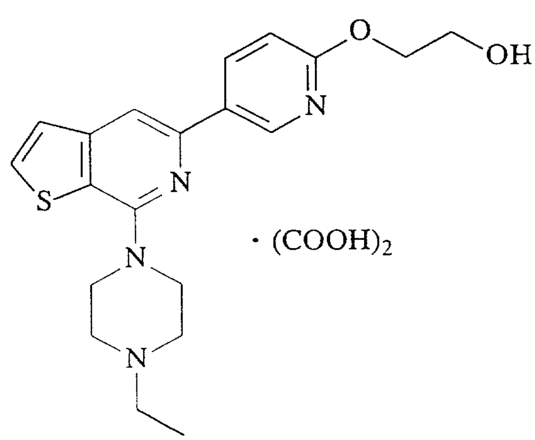
^{1}H-NMR(400MHz,DMSO-d_6); δ(ppm) 1.30(t,J=7.2Hz,3H), 1.30-1.34(m,3H), 3.10-3.25(m,4H), 3.30(s,3H), 3.48-3.68(m,6H), 4.45(d,J=13.6Hz,2H), 5.35-5.43(m,1H), 6.93(d,J=8.8Hz,1H), 7.55(d,J=5.2Hz,1H), 8.02(s,1H), 8.10(d,J=5.2Hz,1H), 8.35(s,1H), 8.43(dd,J=8.8,2.4Hz,1H), 8.93(d,J=2.4Hz,1H).

MS(FAB) m/z 413(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ(ppm) 1.16(t,J=7.2Hz,3H), 1.38(d,J=6.4Hz,3H), 2.52(q,J=7.2Hz,2H), 2.68(t,J=4.8Hz,4H), 3.43(s,3H), 3.56-3.66(m,2H), 3.85(t,J=4.8Hz,4H), 5.46-5.50(m,1H), 6.83(d,J=8.8Hz,1H), 7.34(d,J=5.6Hz,1H), 7.57(d,J=5.6Hz,1H), 7.58(s,1H), 8.25(dd,J=8.8,2.4Hz,1H), 8.88(d,J=2.4Hz,1H).

Example 268 Synthesis of 5-[2-(2-hydroxyethoxy)pyridin-5-yl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine oxalate



In the same manners sequentially as in Examples 161-2 and 20, a yellow oil was obtained from 5-bromo-2-(2-

benzyloxyethoxy)pyridine (610 mg) and 5-bromo-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine (200 mg). To the resulting oil were added methanol (15 ml) and palladium/carbon catalyst (230 mg), and the mixture was reacted in hydrogen atmosphere at room temperature overnight. The resulting residue was basified by adding a 1N aqueous solution of sodium hydroxide thereto, and then extracted with ethyl acetate. The resulting organic layer was washed with brine, dried and evaporated. Sequentially, the resulting residue was purified by NH-silica gel column chromatography (ethyl acetate/hexane system), to give a yellow oil (69 mg, yield; 38%). The resulting oil was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 124-125°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.21(t,J=7.2Hz,3H), 3.01(br,2H), 3.20(br,4H), 3.55-3.62(m,2H), 3.72-3.78(m,2H), 3.89(br,2H), 4.30-4.35(m,2H), 6.93(d,J=8.4Hz,1H), 7.54(d,J=5.2Hz,1H), 7.99(s,1H), 8.07(d,J=5.2Hz,1H), 8.41(dd,J=8.4,2.4Hz,1H), 8.92(d,J=2.4Hz,1H).

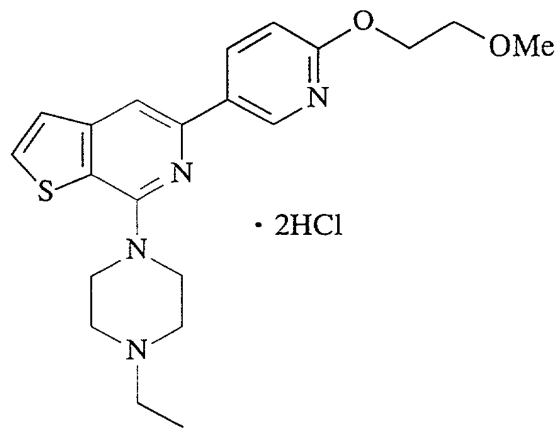
MS(FAB) m/z 385(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 2.52(q,J=7.2Hz,2H), 2.68(t,J=5.2Hz,4H), 3.86(t,J=5.2Hz,4H), 3.96-3.99(m,2H), 4.50-4.54(m,2H), 6.89(d,J=8.8Hz,1H), 7.35(d,J=5.6Hz,1H), 7.59(d,J=5.6Hz,1H), 7.59(s,1H),

8.31(dd,J=8.8,2.4Hz,1H), 8.85(d,J=2.4Hz,1H).

Example 269 Synthesis of 5-[2-(2-methoxyethoxy)pyridin-5-yl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, a colorless oil was obtained (192 mg, yield; 79%) from 5-bromo-2-methoxyethoxypyridine (607 mg) and 5-bromo-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine (200 mg). The resulting oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 116-118°C

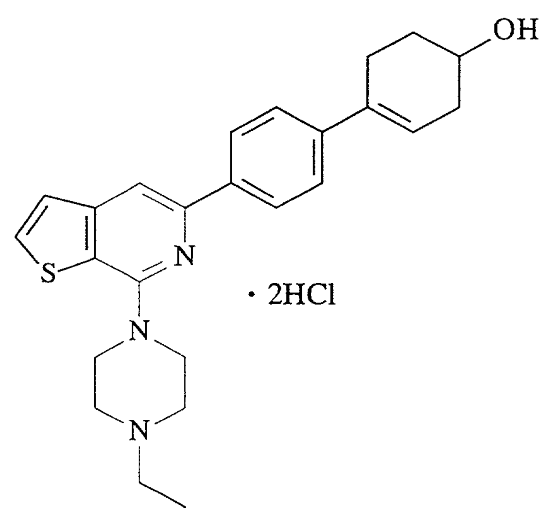
^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.31(t,J=7.2Hz,3H), 3.15-3.35(m,4H), 3.32(s,3H), 3.58-3.64(m,4H), 3.69(t,J=8.0Hz,2H), 4.42-4.48(m,4H), 6.96(d,J=8.4Hz,1H), 7.55(d,J=5.6Hz,1H), 8.02(s,1H), 8.10(d,J=5.6Hz,1H), 8.44(dd,J=8.4,2.4Hz,1H), 8.93(d,J=2.4Hz,1H).

MS(FAB) m/z 399(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 2.52(q,J=7.2Hz,2H), 2.68(t,J=4.8Hz,4H), 3.46(s,3H), 3.79(t,J=4.8Hz,2H), 3.85(t,J=4.8Hz,4H), 4.54(t,J=4.8Hz,2H), 6.89(d,J=8.8Hz,1H), 7.34(d,J=5.6Hz,1H), 7.57(d,J=5.6Hz,1H), 7.58(s,1H), 8.27(dd,J=8.8,2.4Hz,1H), 8.88(d,J=2.4Hz,1H).

<u>Example 270 Synthesis of 5-[4-(4-hydroxycyclohexen-1-yl)phenyl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine hydrochloride</u>



In the same manners sequentially as in Examples 161-2 and 20, an oil was obtained from 1-bromo-4-(4-acetoxycyclohexen-1-yl)benzene (477 mg) and 5-bromo-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine (200 mg). To the resulting oil were added methanol (10 ml) and a 1N aqueous solution of sodium hydroxide (1 ml), and the mixture was heated under reflux for 1 hr. The reaction solution was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and concentrated. The resulting

residue was purified by silica gel column chromatography (hexane/ethyl acetate system), to give a colorless oil (175 mg, yield; 68%). The resulting oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as white crystals.

Hydrochloride:

m.p.; 168-170°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.31(t,J=7.2Hz,3H), 1.60-1.70(m,1H), 2.05-2.15(m,1H), 2.40-2.60(m,2H), 3.19(br,5H), 3.54-3.66(m,5H), 3.80(br,1H), 4.43(d,J=14.0Hz,2H), 6.15(br,1H), 7.53(d,J=8.4Hz,2H), 7.57(d,J=5.2Hz,1H), 8.05(s,1H), 8.08(d,J=5.2Hz,1H), 8.10(d,J=8.4Hz,2H).

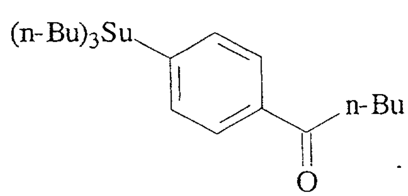
MS(FAB) m/z 420$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.6Hz,3H), 1.82-1.89(m,1H), 2.02-2.07(m,1H), 2.22-2.28(m,1H), 2.53(q,J=7.6Hz,2H), 2.50-2.66(m,3H), 2.70(t,J=5.2Hz,4H), 3.86(t,J=5.2Hz,4H), 4.06-4.11(m,1H), 6.08-6.09(m,1H), 7.34(d,J=5.6Hz,1H), 7.47(d,J=8.8Hz,2H), 7.56(d,J=5.6Hz,1H), 7.68(s,1H), 8.06(d,J=8.8Hz,2H).

Example 271 Synthesis of 7-(1-ethylpiperazin-4-yl)-5-(4-pentanoylphenyl)thieno[2,3-c]pyridine dihydrochloride

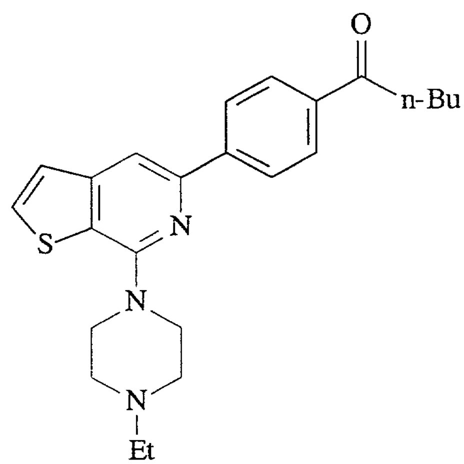
(271-1) 4-Tributylstannylvalerophenone



In the same manner as in Example 161-2, the title compound was obtained as a colorless oil (1.297 mg, yield; 58%) from 4-bromovalerophenone (1.206 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.88(9H,t,J=7.2Hz), 0.95(3H,t,J=7.2Hz), 1.06-1.76(20H,m), 2.95(2H,t,J=7.6Hz), 7.57(2H,d,J=8Hz), 7.87(2H,d,J=8Hz).

(271-2) 7-(1-Ethylpiperazin-4-yl)-5-(4-pentanoylphenyl)thieno[2,3-c]pyridine dihydrochloride



In the same manner as in Example 161-3, the hydrochloride of the title compound was obtained as yellow crystals (118 mg, yield; 68%) from 4-tributylstannylvalerophenone (269 mg) and 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (120 mg).

Hydrochloride:

m.p.; 109-114°C

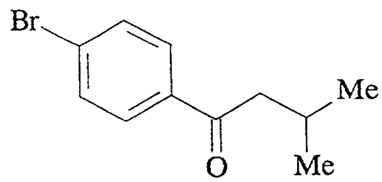
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.90(3H,t,J=7.4Hz), 1.30(3H,t,J=7.2Hz), 1.30-1.40(2H,m), 1.56-1.64(2H,m), 3.03(2H,t,J=7.4Hz), 3.13-3.24(4H,m), 3.56-3.66(4H,m),

4.43(2H,d,J=14Hz), 7.59(1H,d,J=5.4Hz), 8.05(2H,d,J=8.4Hz), 8.10(1H,d,J=5.4Hz), 8.15(1H,s), 8.26(2H,d,J=8.4Hz), 11.30-11.40(1H,br-s).

ESI-Mass; 408(MH^+).

Example 272 Synthesis of 7-(1-ethylpiperazin-4-yl)-5-[4-(3-methylbutanoyl)phenyl]thieno[2,3-c]pyridine dihydrochloride

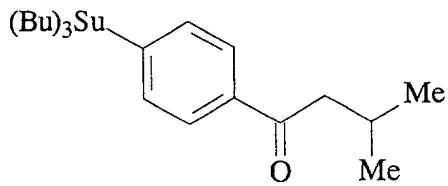
(272-1) 4-Bromoisovalerophenone



Aluminum chloride (32.8 g) was suspended in 1,2-dichloroethane (200 ml), and then under ice-cooling, a solution of bromobenzene (21.6 ml) and isovaleryl chloride (25 ml) in 1,2-dichloroethane (20 ml) was added dropwise thereto and the resulting mixture was stirred for 1 hr. Thereafter, the mixture was stirred at room temperature for 1 hr, and continuously at 60°C for 1 hr. After cooling as it was, the reaction mixture was poured onto ice in small portions. The reaction mixture was extracted with chloroform, and the resulting organic layer was washed with 5N sodium hydroxide and brine, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a brown solid (26.105 g, yield; 53%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.99(6H,d,J=6.8Hz), 2.21-2.37(1H,m), 2.80(2H,d,J=6.8Hz), 7.60(2H,d,J=8.8Hz), 7.82(2H,d,J=8.8Hz).

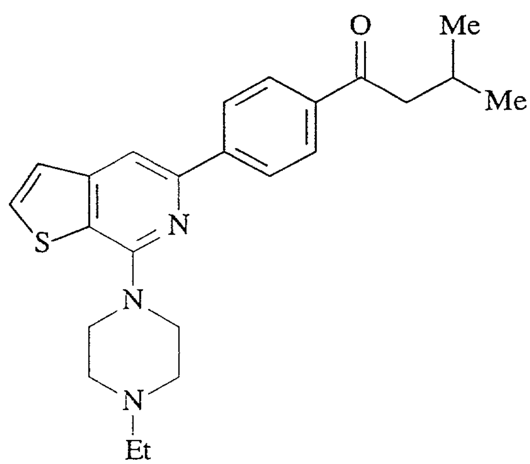
(272-2) 4-Tributylstannylisovalerophenone



In the same manner as in Example 161-2, the title compound was obtained as a colorless oil (1.493 mg, yield; 51%) from 4-bromoisovalerophenone (1.577 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.89(9H,t,J=7.4Hz), 0.99(6H,d,J=6.8Hz), 1.06-1.11(6H,m), 1.28-1.38(6H,m), 1.50-1.58(6H,m), 2.24-2.36(1H,m), 2.82(2H,d,J=7.2Hz), 7.57(2H,d,J=8Hz), 7.86(2H,d,J=8Hz).

(272-3) 7-(1-Ethylpiperazin-4-yl)-5-[4-(3-methylbutanoyl)phenyl]thieno[2,3-c]pyridine dihydrochloride



In the same manner as in Example 161-3, the hydrochloride of the title compound was obtained as yellow crystals (130 mg, yield; 63%) from 4-tributylstannylisovalerophenone (322 mg) and 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (140 mg).

Hydrochloride:

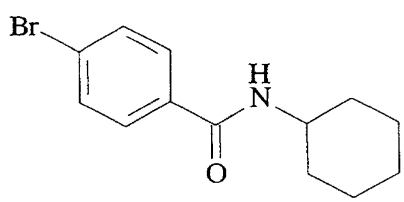
m.p.; 139-141°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.94(6H,d,J=6.4Hz), 1.30(3H,t,J=7.2Hz), 2.11-2.21(1H,m), 2.91(2H,d,J=7.2Hz), 3.13-3.23(4H,m), 3.56-3.66(4H.m), 4.43(2H,d,J=14Hz), 7.59(1H,d,J=5.2Hz), 8.05(2H,d,J=8.4Hz), 8.10(1H,d,J=5.2Hz), 8.15(1H,s), 8.26(2H,d,J=8.4Hz), 11.15-11.25(1H,br-s).

ESI-Mass; 408(MH^+).

Example 273 Synthesis of 7-(1-ethylpiperazin-4-yl)-5-[4-(N-cyclohexylamide)phenyl]thieno[2,3-c]pyridinecarboxamide dihydrochloride

(273-1) 4-Bromo-N-cyclohexylbenzamide

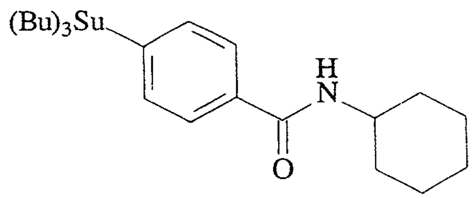


Cyclohexylamine (9.111 g) was dissolved in tetrahydrofuran (100 ml), followed by the addition of 4-bromobenzoyl chloride (5.04 g)/tetrahydrofuran solution (30 ml) under ice-cooling, and the mixture was stirred for 20 min. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was recrystallized from ethyl acetate/hexane, to give the title compound as a pale pink solid (5.236 g, yield; 83%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18-1.28(2H,m), 1.38-1.46(2H,m),

1.73-1.79(2H,m), 2.01-2.06(2H,m), 3.80-3.40(1H,m), 5.70-5.90(1H,m), 7.56(2H,d,J=8Hz), 7.62(2H,d,J=8Hz).

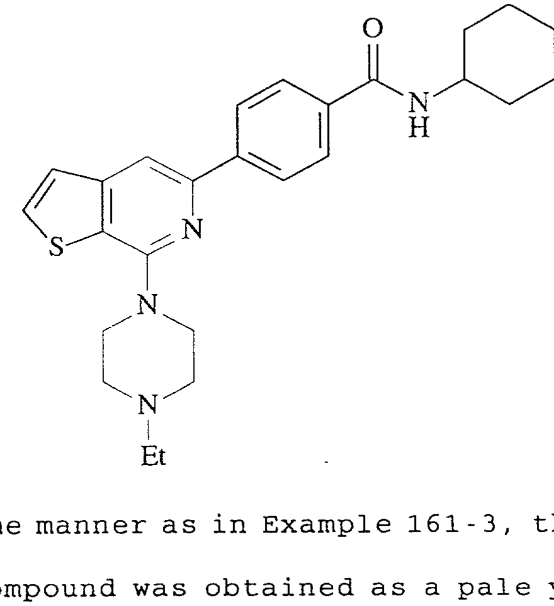
(273-2) 4-Tributylstannyl-N-cyclohexylbenzamide



In the same manner as in Example 161-2, the title compound was obtained as a colorless solid (798 mg, yield; 40%) from 4-bromo-N-cyclohexylbenzamide (1.129 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.88(9H,t,J=7.2Hz), 1.04-2.04(28H,m), 3.59-4.01(1H,m), 5.95(1H,d,J=8.4Hz), 7.52(2H,d,J=8Hz), 7.67(2H,d,J=8Hz).

(273-3) 7-(1-Ethylpiperazin-4-yl)-5-[4-(N-cyclohexylamide)phenyl]thieno[2,3-c]pyridine·dihydrochloride



In the same manner as in Example 161-3, the hydrochloride of the title compound was obtained as a pale yellow amorphous

(yield; 14%) from 4-tributylstannyl-N-cyclohexylbenzamide (457 mg) and 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (228 mg).

Hydrochloride:

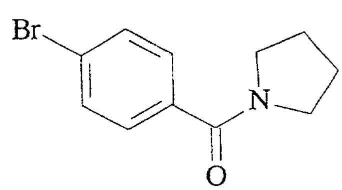
m.p.; 160-165°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.03-1.20(1H,m), 1.29(3H,t,J=7.2Hz), 1.27-1.35(4H,m), 1.57-1.85(3H,m), 3.14-3.23(4H,m), 3.56(2H,t,J=14Hz), 3.63(2H,t,J=14Hz), 3.63(2H,d,12Hz), 3.70-3.82(1H,m), 4.43(2H,d,J=14Hz), 7.58(1H,d,J=5.6Hz), 7.94(2H,d,J=8.8Hz), 8.09(1H,d,J=5.6Hz), 8.12(1H,s), 8.19(2H,d,J=8.8Hz), 8.26(1H,d,J=8Hz), 10.85-10.95(1H,br-s).

ESI-Mass; 449(MH$^+$).

Example 274 Synthesis of 7-(1-ethylpiperazin-4-yl)-5-[4-(pyrrolidinyl-1-carbonyl)phenyl]thieno[2,3-c]pyridine dihydrochloride

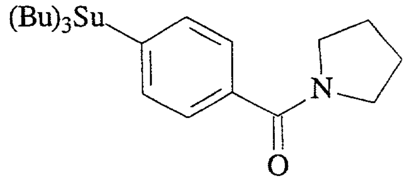
(274-1) (4-Bromobenzoyl)pyrrolidine



In the same manner as in Example 273-1, the titled compound was obtained as a colorless solid (5.07 g, yield; 87%) from 4-bromobenzoyl chloride (5.027 g) and pyrrolidine (6.543 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.89(2H,qui,J=6.8Hz), 1.97(2H,qui,J=6.8Hz), 3.41(2H,t,J=6.8Hz), 3.63(2H,t,J=6.8Hz), 7.40(2H,d,J=8.8Hz), 7.54(2H,d,J=8.8Hz).

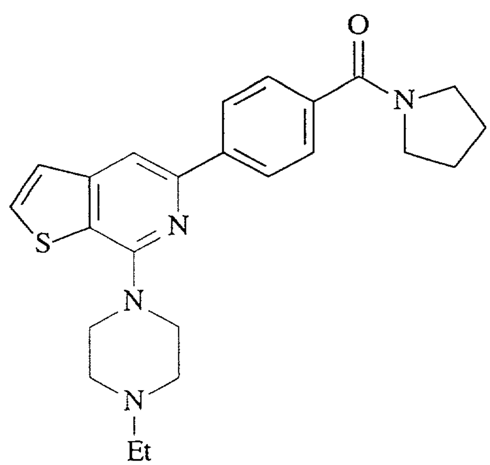
(274-2) (4-Tributylstannylbenzoyl)pyrrolidine



In the same manner as in Example 161-2, the title compound was obtained as a colorless oil (976 mg, yield; 53%) from (4-bromobenzoyl)pyrrolidine (1.574 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.88(9H,t,J=7.4Hz), 1.03-1.08(6H,m), 1.29-1.37(6H,m), 1.49-1.56(6H,m), 1.84-1.99(4H,m), 3.45(2H,t,J=6.6Hz), 3.65(2H,t,J=7Hz), 7.44(2H,d,J=8Hz), 7.48(2H,d,J=8Hz).

(274-3) 7-(1-Ethylpiperazin-4-yl)-5-[4-(pyrrolidinyl-1-carbonyl)phenyl]thieno[2,3-c]pyridine dihydrochloride



In the same manner as in Example 161-3, the hydrochloride of the title compound was obtained as a yellow amorphous (183 mg, yield; 57%) from (4-tributylstannylbenzoyl)pyrrolidine (564 mg) and 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (223 mg).

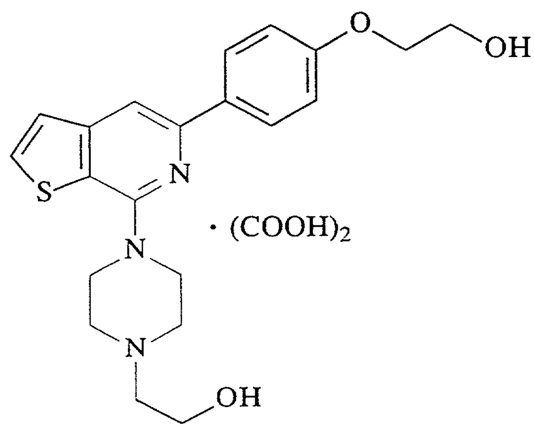
Hydrochloride:

m.p.; 143-146°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.29(3H,t,J=7.2Hz), 1.76-1.90(4H,m), 3.14-3.23(4H,m), 3.42(4H,t,J=6.4Hz), 3.47(4H,t,J=6.8Hz), 3.57(2H,d,J=8.4Hz), 3.62(2H,d,J=12Hz), 4.42(2H,d,J=14Hz), 7.57(1H,d,J=5.6Hz), 8.09(1H,d,J=5.6Hz), 8.10(1H,s), 8.18(2H,d,J=8.8Hz), 10.95-11.05(1H,br-s).

ESI-Mass; 421(MH^+).

Example 275 Synthesis of 5-[4-(2-hydroxyethoxy)phenyl]-7-[4-(2-hydroxyethyl)piperazin-1-yl]thieno[3,2-c]pyridine oxalate



5-(4-Hydroxyphenyl)-7-(piperazin-1-yl)thieno[2,3-c]pyridine (139 mg) was dissolved in DMF (6 ml), followed by the addition of 60% sodium hydride (33 mg) and ethyl bromoacetate (0.068 ml), and the mixture was reacted at 60°C for 1 hr. The reaction solution was poured into an aqueous solution of saturated ammonium chloride and extracted with ethyl acetate. The organic layer was washed with water, dried and evaporated. To the resulting residue were added

tetrahydrofuran (10 ml) and 1.0 M lithium aluminum hydride/tetrahydrofuran solution (0.9 ml), and the mixture was reacted under ice-cooling for 10 min. To the resulting reaction solution were then sequentially added water (0.03 ml), a 5N aqueous solution of sodium hydroxide (0.03 ml) and water (0.09 ml), and the mixture was stirred at room temperature for 30 min. The resulting residue was filtered, washed with ethyl acetate and then purified by NH-silica gel chromatography (hexane/ethyl acetate system), to give a colorless oil (30 mg, yield; 21%). The resulting oil was converted into an oxalate in a conventional manner, to obtain the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 105-107°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 2.93(br,2H), 3.12(br,4H), 3.70(t,J=4.8Hz,2H), 3.75(t,J=4.8Hz,2H), 3.85(br,4H), 4.05(t,J=4.8Hz,2H), 7.04(d,J=8.8Hz,2H), 7.51(d,J=5.6Hz,1H), 7.90(s,1H), 8.01(d,J=5.6Hz,1H), 8.07(d,J=8.8Hz,2H).

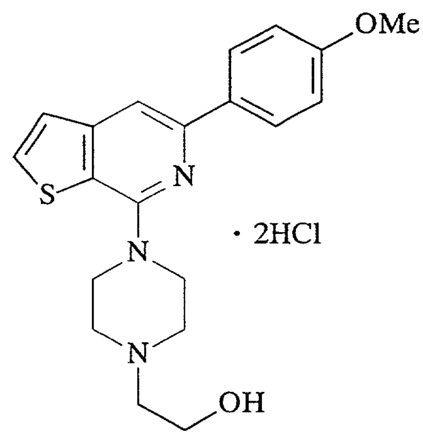
MS(FAB) m/z 400(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 2.66(t,J=5.6Hz,2H), 2.76(t,J=4.8Hz,4H), 3.69(t,J=5.6Hz,2H), 3.82(t,J=4.8Hz,4H), 4.00(t,J=4.4Hz,2H), 4.15(t,J=4.4Hz,2H), 7.01(d,J=8.8Hz,2H), 7.34(d,J=5.6Hz,1H), 7.56(d,J=5.6Hz,1H), 7.64(s,1H), 8.05(d,J=8.8Hz,2H).

Example 276 Synthesis of 5-(4-methoxyphenyl)-7-[4-(2-

hydroxyethyl)piperazin-1-yl]thieno[2,3-c]pyridine hydrochloride



DMSO (6 ml) and 4-hydroxyethylpiperazine (6 ml) were added to 7-chloro-5-(4-methoxyphenyl)thieno[2,3-c]pyridine (920 mg), and the mixture was reacted at 140°C overnight. The reaction solution was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and evaporated. The resulting residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate system), to give a yellow oil (350 mg, yield; 28%). The resulting oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 129-131°C

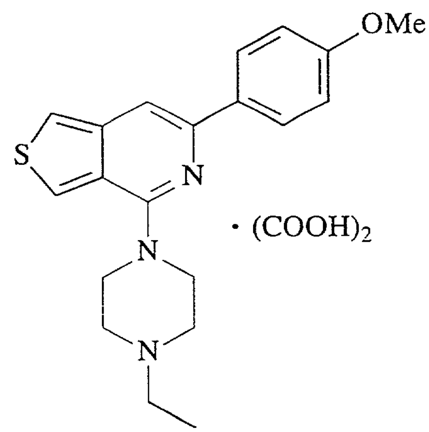
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 3.25-3.32(m,4H), 3.56-3.70(m,6H), 3.84(s,3H), 4.41(t,J=14.4Hz,2H), 7.05(d,J=8.8Hz,2H), 7.54(d,J=5.6Hz,1H), 7.96(s,1H), 8.05(d,J=5.6Hz,1H), 8.09(d,J=8.8Hz,2H).

MS(FAB) m/z 370$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz, $CDCl_3$); δ (ppm) 2.65(t,J=5.2Hz,2H), 2.76(t,J=5.2Hz,4H), 3.69(t,J=5.2Hz,2H), 3.82(t,J=5.2Hz,4H), 3.87(s,3H), 6.99(d,J=8.8Hz,2H), 7.33(d,J=5.6Hz,1H), 7.56(d,J=5.6Hz,1H), 7.63(s,1H), 8.04(d,J=8.8Hz,2H).

Example 277 Synthesis of 4-(4-ethylpiperazin-1-yl)-6-(4-methoxyphenyl)thieno[3,4-c]pyridine oxalate



In the same manner as in Example 10, the free compound of the title compound was obtained (57 mg, yield; 13%) from 4-chloro-6-(4-methoxyphenyl)thieno[3,4-c]pyridine (356 mg) and ethylpiperazine (6 ml). The resulting free compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

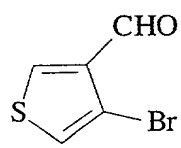
^{1}H-NMR(400MHz, DMSO-d_6); δ (ppm) 1.25(t,J=7.2Hz,3H), 3.12(q,J=7.2Hz,2H), 3.32(br,4H), 3.81(s,3H), 3.93(br,4H), 7.01(d,J=8.8Hz,2H), 7.59(s,1H), 7.93(d,J=2.4Hz,1H), 8.04(d,J=8.8Hz,2H), 8.46(br,1H).

Free compound:

^{1}H-NMR(400MHz, $CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.73(br,4H), 3.85(br,4H), 3.87(s,3H), 6.97(d,J=8.4Hz,2H), 7.36(s,1H), 7.52(d,J=3.2Hz,1H), 7.86(d,J=3.2Hz,1H), 8.04(d,J=8.8Hz,2H).

Example 278 Synthesis of 4-(4-ethylpiperazin-1-yl)-6-[4-(2-hydroxyethoxy)phenyl]thieno[3,4-c]pyridine oxalate

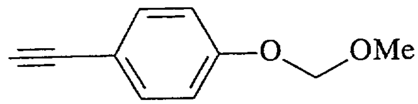
(278-1) 3-Formyl-4-bromothiophene



3,4-Dibromothiophene (30 g) was dissolved in diethyl ether (150 ml), followed by the addition of 2.5M n-butyl lithium (60 ml) at -78°C. Subsequently, DMF(14 ml)/diethyl ether solution (50 ml) was added thereto, and the mixture was stirred for 3 hr with heating under reflux. The reaction solution was poured into 1N hydrochloric acid, and then extracted with ethyl acetate. The resulting organic layer was washed with an aqueous solution of saturated sodium bicarbonate and brine, dried and evaporated. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system), to give a colorless oil (14.7 g, yield; 62%).

^{1}H-NMR(400MHz, $CDCl_3$); δ (ppm) 7.37(d,J=3.6Hz,1H), 8.17(d,J=3.6Hz,1H), 9.96(s,1H).

(278-2) 4-Methoxymethoxy-1-ethynylbenzene



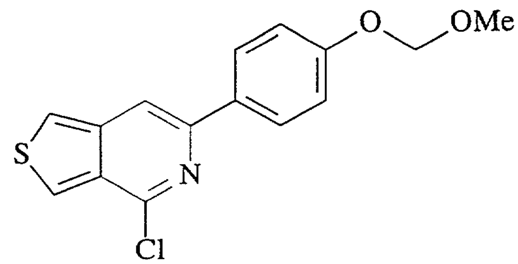
Paraiodophenol (25 g) was dissolved in DMF (100 ml), followed by the addition of potassium t-butoxide (25 g) and methoxymethyl chloride (13 ml), and the mixture was reacted at 60°C overnight. The reaction solution was poured into water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried and evaporated. The resulting residue was subjected to a silica gel short column, to give 4-methoxymethoxy-1-iodobenzene as an oil (26.5 g, yield; 88%).

To the resulting oil (26.5 g) were added trimethylsilylacetylene (28 ml), pyridine (50 ml), triethylamine (100 ml), CuI (0.35 g) and $Pd(PPh_3)_2Cl_2$ (0.7 g), and the mixture was reacted at 60°C overnight. The reaction solution was poured into 1N hydrochloric acid, and the organic layer was washed with an aqueous solution of saturated sodium bicarbonate and brine, dried and evaporated, to give an oil.

The resulting oil was dissolved in a methanol (90 ml), followed by the addition of a 1N aqueous solution of sodium hydroxide (10 ml), and the mixture was heated under reflux for 1 hr. The reaction solution was partitioned between ethyl acetate and water. The organic phase was washed with water, dried and concentrated. The solvent was evaporated, to give the title compound as a yellow oil (11.4 g, yield; 70%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 3.00(s,1H), 3.47(s,3H), 5.18(s,2H), 6.98(d,J=8.8Hz,2H), 7.42(d,J=8.8Hz,2H).

(278-3) 4-Chloro-6-[4-(methoxymethoxy)phenyl]thieno[3,4-c]pyridine



3-Formyl-4-bromothiophene (14.7 g) was dissolved in DMF (100 ml), followed by the addition of triethylamine (100 ml), CuI (0.25 g), $Pd(PPh_3)_2Cl_2$ (0.5 g) and 4-methoxymethoxy-1-ethynylbenzene (11.4 g), and the mixture was reacted at 70°C overnight. The reaction solution was filtered through Celite, poured into 1N hydrochloric acid, and then extracted with ethyl acetate. The organic layer was washed with an aqueous solution of saturated sodium bicarbonate and brine, dried and evaporated. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system), to give 3-{[4-(methoxymethoxy)phenyl]ethynyl}-4-formylthiophene as a colorless oil (12.8 g, yield; 47%).

The resulting oil (12.8 g) was dissolved in ethanol (150 ml), followed by the addition of water (50 ml), hydroxylamine hydrochloride (4.9 g) and sodium acetate (7.7 g), and the mixture was heated under reflux for 3 hr. The reaction solution was evaporated, and then extracted with ethyl acetate. The organic layer was washed with brine, dried and evaporated, and then purified by silica gel column chromatography (hexane/ethyl

acetate system), to give 3-{[4-(methoxymethoxy)phenyl]ethynyl}-4-formylthiophene oxime as a brown oil (10.5 g, yield; 77%).

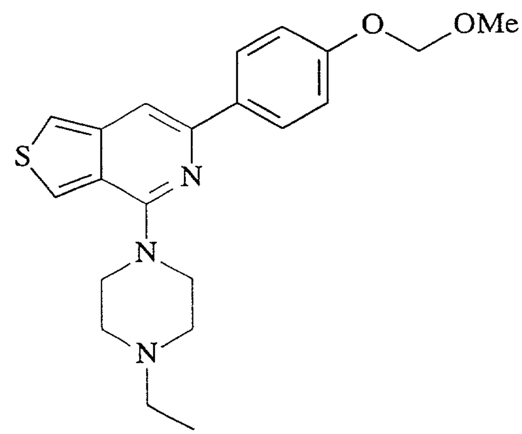
The resulting brown oil (10.5 g) was dissolved in n-butanol (100 ml), followed by the addition of water (25 ml) and potassium carbonate (7.5 g), and the resulting mixture was reacted with heating under reflux overnight. The reaction solution was evaporated and extracted with ethyl acetate. The organic layer was washed with brine, dried and evaporated, and then purified by silica gel column chromatography (dichloromethane/methanol system), to give 6-[4-(methoxymethoxy)phenyl]thieno[3,4-c]pyridine N-oxide as a yellow oil (2.6 g, yield; 25%).

The resulting yellow oil (2.6 g) was dissolved in chloroform (100 ml), followed by the addition of diisopropylamine (16 ml) and phosphorus oxychloride (1.7 ml), and the mixture was reacted with heating under reflux for 20 min. The reaction solution was ice-cooled, followed by the addition of methanol and evaporation. The resulting residue was partitioned between ethyl acetate and water, and the resulting ethyl acetate layer was washed with an aqueous solution of saturated sodium bicarbonate and brine, dried and evaporated. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system), to give the title compound as a colorless oil (1.1 g, yield; 39%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 3.50(s,3H), 5.23(s,2H), 7.12(d,J=8.8Hz,2H), 7.53(s,1H), 7.65(d,J=8.8Hz,2H),

7.74(s,1H)、8.79(s,1H).

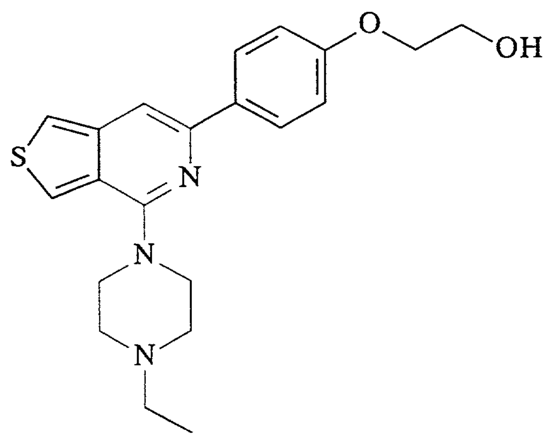
(278-4) 4-(4-Ethylpiperazin-1-yl)-6-(4-methoxymethoxyphenyl)thieno[3,4-c]pyridine or compound identified by the following analysis data and synthetic procedures



In the same manner as in Example 1, a yellow oil was obtained (695 mg, yield; 51%) from 4-chloro-6-(4-methoxymethoxyphenyl)thieno[3,4-c]pyridine (1.1 g), potassium carbonate (1 g), ethylpiperazine (0.8 ml) and DMF (10 ml).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.53(q,J=7.2Hz,2H), 2.70(t,J=4.8Hz,4H), 3.56(s,3H), 3.84(t,J=4.8Hz,4H), 5.22(s,2H), 7.10(d,J=8.8Hz,2H), 7.35(d,J=0.8Hz,1H), 7.52(d,J=3.2Hz,1H), 7.86(dd,J=3.2,0.8Hz,1H), 8.02(d,J=8.8Hz,2H).

(278-5) 4-(4-Ethylpiperazin-1-yl)-6-[4-(2-hydroxyethoxy)phenyl]thieno[3,4-c]pyridine or compound identified by the following analysis data and synthetic procedures



4-(4-Ethylpiperazin-1-yl)-6-[4-(methoxymethoxy)phenyl]thieno[3,4-c]pyridine (695 mg) was dissolved in ethanol (10 ml), followed by the addition of a 5N aqueous solution of hydrochloric acid (1 ml), and the mixture was reacted for 1 hr with heating under reflux. The reaction solution was neutralized with a 1N aqueous solution of sodium hydroxide and then extracted with ethyl acetate. The organic layer was washed with brine, dried and evaporated, and then purified by silica gel column chromatography (dichloromethane/methanol system), to give 4-(4-ethylpiperazin-1-yl)-6-(4-hydroxyphenyl)thieno[3,4-c]pyridine as a yellow oil (70 mg, yield; 11%).

4-(4-Ethylpiperazin-1-yl)-6-(4-hydroxyphenyl)thieno[3,4-c]pyridine (70 mg) was dissolved in DMF (10 ml), followed by the addition of 2-bromoethoxy(t-butyl)dimethylsilane (300 mg) and 60% sodium hydride (33 mg), and the mixture was reacted at 60°C overnight. The reaction solution was poured into an aqueous solution of saturated ammonium chloride and extracted with ethyl acetate. The

organic layer was washed with water and brine, dried and evaporated, to give 4-(4-ethylpiperazin-1-yl)-6-{4-[2-(t-butyl)dimethylsilyloxyethoxy]phenyl}thieno[3,4-c]pyridine as an oil. The resulting oil was then dissolved in tetrahydrofuran (5 ml), followed by the addition of 1.0M tetrabutylammonium fluoride/tetrahydrofuran solution (5 ml), and the mixture was stirred at room temperature for 1 hr. The reaction solution was partitioned between ethyl acetate and water. The organic layer was washed with water, dried and concentrated. The resulting residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate system), to give a colorless oil (18 mg, yield; 23%). The resulting oil was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 130°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.27(t,J=7.2Hz,3H), 3.19(br,4H), 3.39(br,6H), 3.74(br,2H), 4.04(t,J=4.8Hz,2H), 7.01(d,J=8.8Hz,2H), 7.61(s,1H), 7.94(d,J=2.8Hz,1H), 8.03(d,J=8.8Hz,2H), 8.48(d,J=2.8Hz,1H).

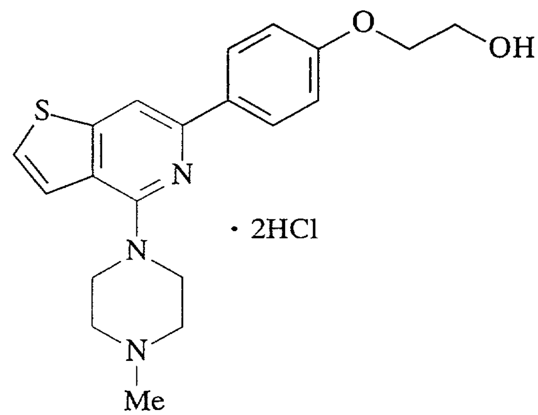
MS(FAB) m/z 384$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.20(t,J=7.2Hz,3H), 2.58(q,J=7.2Hz,2H), 2.77(br,4H), 3.89(br,4H), 3.99(t,J=4.4Hz,2H), 4.15(t,J=4.0Hz,2H), 6.99(d,J=8.8Hz,2H), 7.36(s,1H), 7.53(d,J=3.2Hz,1H), 7.85(d,J=3.2Hz,1H),

8.03(d,J=8.8Hz,2H).

Example 279 Synthesis of 4-(4-methylpiperazin-1-yl)-6-[4-(2-hydroxyethoxy)phenyl]thieno[3,2-c]pyridine hydrochloride



4-(4-Methylpiperazin-1-yl)-6-(4-hydroxyphenyl)thieno[3,2-c]pyridine (413 mg) obtained from 4-chloro-6-(4-methoxyphenyl)thieno[3,2-c]pyridine and N-methylpiperazine in the same manner as in Example 289-6 was dissolved in DMF (10 ml), followed by the addition of potassium carbonate (526 mg) and 2-bromoethanol (0.18 ml). The resulting mixture was stirred at 80°C for 2 days, and then the resulting reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and evaporated. The resulting residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate system), to give a yellow oil (202 mg, yield; 43%). The resulting oil was converted into a hydrochloride in a conventional manner, to give the title compound as yellow crystals.

Hydrochloride:

m.p.; 148-150°C

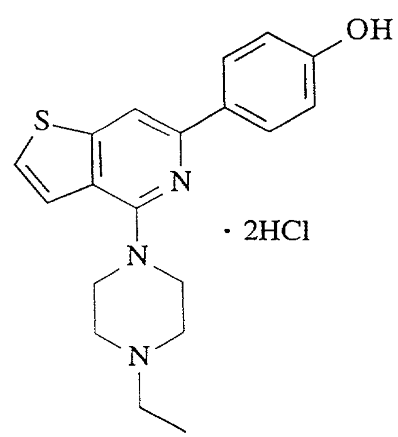
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 2.85(d,J=4.4Hz,3H), 3.27-3.33(m,2H), 3.47-3.55(m,4H), 3.75(t,J=4.8Hz,2H), 4.00-4.06(m,2H), 4.21(d,J=13.2Hz,2H), 7.04(d,J=8.8Hz,2H), 7.61(d,J=5.6Hz,1H), 7.78(d,J=5.6Hz,1H), 8.10(d,J=8.8Hz,2H), 8.18(s,1H).

MS(FAB) m/z 370$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 2.39(s,3H), 2.66(t,J=4.8Hz,4H), 3.69(t,J=4.8Hz,4H), 3.99(t,J=4.8Hz,2H), 4.14(t,J=4.8Hz,2H), 7.00(d,J=8.8Hz,2H), 7.32(d,J=5.6Hz,1H), 7.39(d,J=5.6Hz,1H), 7.72(s,1H), 8.05(d,J=8.8Hz,2H).

Example 280 Synthesis of 4-(4-ethylpiperazin-1-yl)-6-(4-hydroxyphenyl)thieno[3,2-c]pyridine hydrochloride



4-(4-Ethylpiperazin-1-yl)-6-(4-methoxyphenyl)thieno[3,2-c]pyridine (1.85 g) was dissolved in 48% hydrobromic acid (15 ml), and the mixture was reacted for 6hr with heating under reflux. The reaction solution was ice-cooled, and then basified by adding a 8N aqueous solution of sodium hydroxide thereto. A 28% aqueous solution of ammonia

was added to the resulting solution, followed by the extraction with ethyl acetate. The resulting organic layer was washed with water, dried and evaporated. The resulting crystals were washed with hexane and subsequently with diethyl ether, and then dried, to give white crystals (1.44 g, yield; 81%). The resulting crystals were converted into a hydrochloride in a conventional manner, to give the title compound as white crystals.

Hydrochloride:

m.p.; 173-175°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.31(t,J=7.2Hz,3H), 3.13-3.30(m,4H), 3.49-3.60(m,4H), 4.19(d,J=14.0Hz,2H), 6.88(d,J=8.8Hz,2H), 7.60(d,J=5.6Hz,1H), 7.77(d,J=5.6Hz,1H), 7.79(d,J=8.8Hz,2H), 8.11(s,1H).

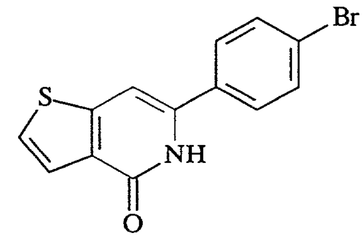
MS(FAB) m/z 340(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.06(t,J=7.2Hz,3H), 2.41(q,J=7.2Hz,2H), 2.59(t,J=4.8Hz,4H), 3.54(t,J=4.8Hz,4H), 6.84(d,J=8.8Hz,2H), 7.48(d,J=5.6Hz,1H), 7.66(d,J=5.6Hz,1H), 7.98(d,J=8.8Hz,2H), 9.64(s,1H).

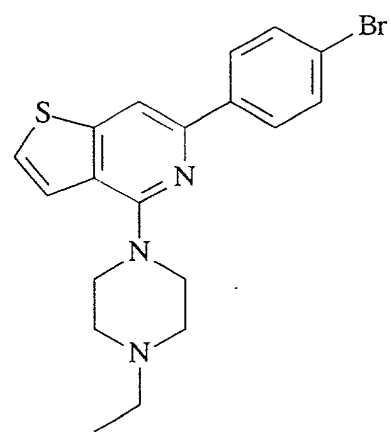
Example 281 Synthesis of 4-(4-ethylpiperazin-1-yl)-6-[4-(1-hydroxyethyl)phenyl]thieno[3,2-c]pyridine oxalate

(281-1) 6-(4-Bromophenyl)-5H-thieno[3,2-c]pyridin-4-one



To a solution of N-methyl-2-methylthiophene-3-carboxamide (13.0 g) in tetrahydrofuran (130 ml) was dropwise added 2.5 M butyl lithium (74 ml) at -70°C. The reaction solution was stirred at -70°C for 2 hr, followed by the addition of 4-bromobenzonitrile (15.3 g) at once. After the dry ice/acetone bath was removed, the reaction mixture was back to room temperature. Three hours later, an aqueous solution of saturated ammonium chloride and ether were added thereto, and then the resulting mixture was further stirred for 1 hr. The resulting white precipitates were collected by filtration, and washed with water, ether and n-hexane in this order. The resulting product was dried to give the title compound (4.9 g, yield; 19%).

(281-2) 4-(4-Ethylpiperazin-1-yl)-6-(4-bromophenyl)thieno[3,2-c]pyridine



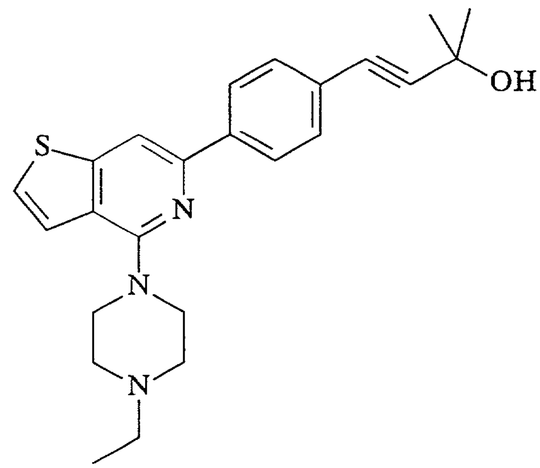
6-(4-Bromophenyl)-5H-thieno[3,2-c]pyridin-4-one (4.87 g) was added to phosphorus oxychloride (30 ml), and the resulting mixture was heated at 100°C for 3 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water. The organic layer was washed with water, an aqueous solution of saturated sodium bicarbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, to give 4-chloro-6-(4-bromophenyl)thieno[3,2-c]pyridine.

Then, the resulting compound was heated with N-ethylpiperazine (50 ml) at 100°C for 2 hr. The reaction mixture was evaporated, and to the resulting residue were added potassium carbonate and water, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was removed, and the resulting residue was purified by NH-silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a pale brown oil (3.76 g, yield; 58.8%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(3H,t,J=7.2Hz), 2.53(2H,q,J=7.2Hz), 2.68(4H,br), 3.71(4H,br), 7.37(1H,d,J=5.6Hz), 7.41(1H,d,J=5.6Hz), 7.56(2H,d,J=8.4Hz), 7.76(1H,s), 7.96(2H,d,J=8.4Hz).

(281-3) 6-[4-(3,3-Dimethyl-3-hydroxy-1-propynyl)phenyl]-(4-ethylpiperazin-1-yl)thieno[3,2-c]pyridine or compound identified by the following analysis data and synthetic

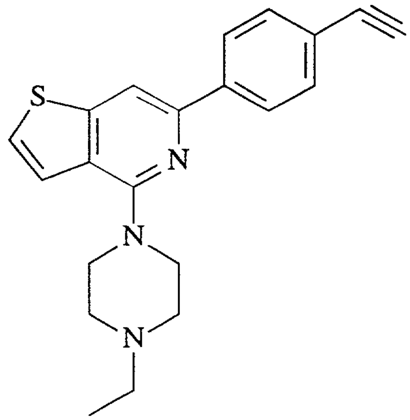
procedures



6-(4-Bromophenyl)-4-(4-ethylpiperazin-1-yl)thieno[3,2-c]pyridine (0.96 g) was heated under reflux in the presence of bistriphenylphosphine dichloride (48 mg), triphenylphosphine (174 mg) and cuprous iodide (46 mg), in 2-methyl-3-butyn-2-ol (0.26 g), pyridine (15 ml) and triethylamine (30 ml) for 1.5 hr. The reaction solution was evaporated, and the resulting residue was purified by NH-silica gel column chromatography (ethyl acetate/hexane system), to give 0.80 g of the title compound as a pale yellow oil.

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(3H,t,J=7.2Hz), 1.63(6H,s), 2.53(2H,q,J=7.2Hz), 2.68(4H,br), 3.70(4H,br), 7.36(1H,d,J=5.6Hz), 7.41(1H,d,J=5.6Hz), 7.47(2H,d,J=8.4Hz), 7.78(1H,s), 8.03(2H,d,J=8.4Hz).

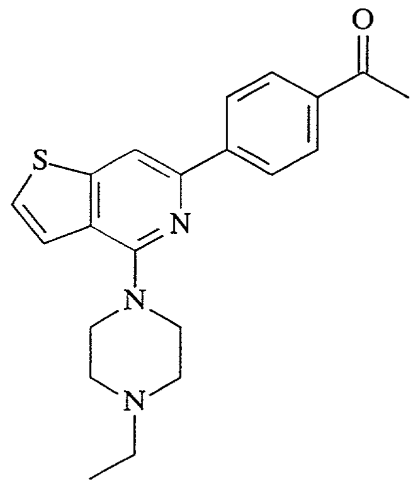
(281-4) 6-(4-Ethynylphenyl)-(4-ethylpiperazin-1-yl)thieno[3,2-c]pyridine



6-[4-(3,3-Dimethyl-3-hydroxy-1-propynyl)phenyl]-(4-ethylpiperazin-1-yl)thieno[3,2-c]pyridine (0.80 g) was dissolved in 1-butanol (15 ml), followed by the addition of potassium hydroxide (0.47 g), and the mixture was heated under reflux for 20 min. The reaction solution was evaporated, and the resulting residue was partitioned between ethyl acetate and water, and then extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was removed, and the resulting residue was dissolved in ether, and then filtered through NH-silica gel. The resulting filtrate was concentrated, to give 0.59 g of the title compound as a pale yellow oil.

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(3H,t,J=7.2Hz), 2.53(2H,q,J=7.2Hz), 2.68(4H,br), 3.13(1H,s), 3.70(4H,br), 7.37(1H,d,J=5.6Hz), 7.41(1H,d,J=5.6Hz), 7.58(2H,d,J=8.4Hz), 7.80(1H,s), 8.06(2H,d,J=8.4Hz).

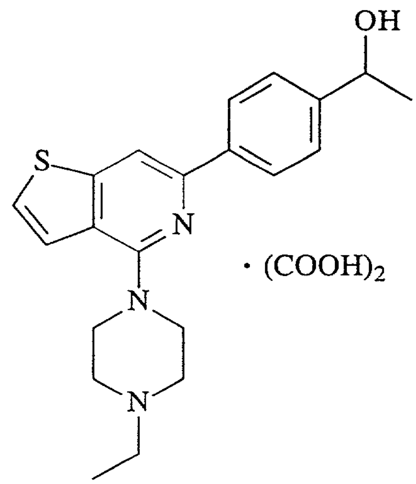
(281-5) 6-(4-Acetylphenyl)-(4-ethylpiperazin-1-yl)thieno[3,2-c]pyridine



6-(4-Ethynylphenyl)-(4-ethylpiperazin-1-yl)thieno[3,2-c]pyridine (0.59 g) was reacted in formic acid (15 ml) at 100°C for 12 hr. The reaction solution was evaporated, basified with an aqueous solution of potassium carbonate, and then extracted with ethyl acetate. The organic layer was washed with water and brine, dried and concentrated. The resulting residue was purified by NH-silica gel column chromatography (ethyl acetate/hexane system), to give 0.37 g of the title compound as a pale yellow oil.

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(3H,t,J=7.2Hz), 2.56(2H,q,J=7.2Hz), 2.64(3H,s), 2.73(4H,br), 3.13(1H,s), 3.73(4H,br), 7.40-7.43(2H,m), 7.86(1H,s), 8.04(1H,s), 8.10(2H,d,J=8.4Hz).

(281-6) 4-(4-Ethylpiperazin-1-yl)-6-[4-(1-hydroxyethyl)phenyl]thieno[3,2-c]pyridine



6-(4-Acetylphenyl)-(4-ethylpiperazin-1-yl)thieno[3,2-c]pyridine (0.37 g) was dissolved in methanol (10 ml), followed by the addition of sodium tetrahydroborate (50 mg) at room temperature. The resulting mixture was reacted for 30 min. The reaction solution was concentrated, and the resulting residue was partitioned between ethyl acetate and water. The organic layer was washed with water and brine, dried and concentrated. The resulting residue was purified by NH-silica gel column chromatography (ethyl acetate), to give 0.31 g of the title compound as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 1.34(d,J=6.0Hz,3H), 2.54(q,J=7.2Hz,2H), 2.70(m,4H), 3.71(m,4H), 4.96(q,J=6.4Hz,1H), 7.35(d,J=5.6Hz,1H), 7.41(d,J=5.6Hz,1H), 7.47(d,J=8.0Hz,2H), 7.78(s,1H), 8.07(d,J=8.0Hz,2H).

The resulting free compound was converted into an oxalate in a conventional manner, to give 0.29 g of the title compound

as a white powder.

Oxalate:

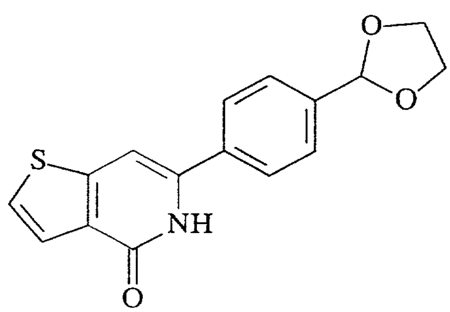
m.p.; 134-135°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.25(t,J=7.2Hz,3H), 1.36(d,J=6.0Hz,3H), 3.11(q,J=7.2Hz,2H), 3.31(m,4H), 3.80(m,4H), 4.78(q,J=6.4Hz,1H), 7.44(d,J=8.4Hz,2H), 7.63(d,J=5.6Hz,1H), 7.81(d,J=5.6Hz,1H), 8.09(d,J=8.4Hz,2H), 8.22(s,1H).

MS(FAB) m/z 368(M+H)$^+$.

Example 282 Synthesis of 4-(4-ethylpiperazin-1-yl)-6-[4-(1-hydroxypropyl)phenyl]thieno[3,2-c]pyridine oxalate

(282-1) 6-[4-(1,3-Dioxolan-2-yl)phenyl]-5H-thieno[3,2-c]pyridin-4-one

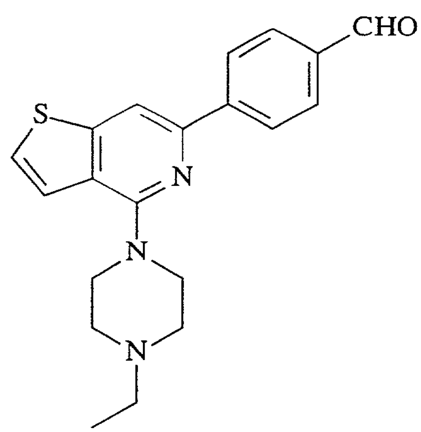


To a solution of N-methyl-2-methylthiophene-3-carboxamide (18.5 g) in tetrahydrofuran (350 ml) was dropwise added 2.5M n-butyl lithium (100 ml) at -70°C. The resulting solution was stirred at -70°C for 1.5 hr, followed by the addition of a solution of 4-(1,3-dioxolan-2-yl)benzonitrile (20.9 g) in tetrahydrofuran (100 ml) at once. After the dry ice/acetone bath was removed, the reaction mixture was back to room temperature. Three hours later, an aqueous solution of

saturated ammonium chloride was added thereto, and the organic layer was separated, washed with water and dried. The filtrate was concentrated, and the resulting solid was washed with ethyl acetate, tetrahydrofuran/ether and n-hexane in this order. The resulting solid was then dried, to give the title compound as white crystals (6.24 g, yield; 31.7%).

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 3.94-4.10(4H,m), 5.79(1H,s), 7.24(1H,s), 7.48-7.56(3H,m), 7.63(2H,d,J=5.6Hz), 7.78(2H,d,J=8.4Hz), 11.67(1H,br-s).

<u>(282-2) 4-(4-Ethylpiperazin-1-yl)-6-(4-formylphenyl)thieno[3,2-c]pyridine</u>



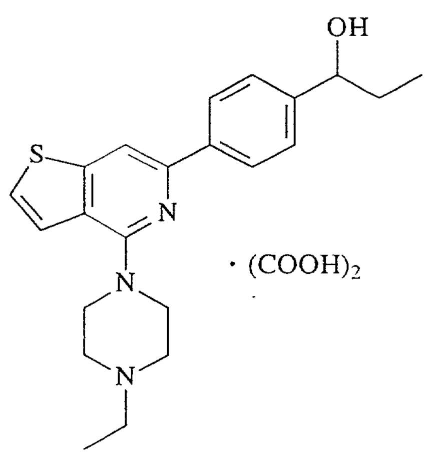
Phosphorus oxychloride (22.7 g) was added to 6-[4-(1,3-dioxolan-2-yl)phenyl]-5H-thieno[3,2-c]pyridin-4-one (6.2 g) at room temperature, and the mixture was reacted at 70°C for 2 hr. The reaction solution evaporated, and to the resulting residue was added an aqueous solution of potassium carbonate, and then the resulting mixture was extracted with ethyl acetate and dried. The solvent was evaporated, to give 4-chloro-6-[4-(1,3-dioxolan-2-yl)phenyl]-5H-thieno[3,2-

c]pyridine.

Then, the resulting compound was reacted with N-ethylpiperazine (40 ml) at 120°C for 12 hr. The reaction solution was evaporated, and the resulting residue was extracted with ethyl acetate. The organic layer was extracted with a 2N aqueous solution of hydrochloric acid (100 ml), and then treated at 50°C for 1 hr. The reaction solution was cooled, basified with a 8N aqueous solution of sodium hydroxide and then extracted with ethyl acetate. The organic layer was washed with water and brine, dried and concentrated. The resulting residue was purified by silica gel column chromatography (toluene/acetone system), to give 0.40 g of the title compound as a pale yellow oil.

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.54(q,J=7.2Hz,2H), 2.70(m,4H), 3.73(m,4H), 7.41-7.44(m,2H), 7.88(s,1H), 7.96(d,J=8.4Hz,2H), 8.25(d,J=8.4Hz,2H), 10.07(s,1H).

(282-3) 4-(4-Ethylpiperazin-1-yl)-6-[4-(1-hydroxypropyl)phenyl]thieno[3,2-c]pyridine



To a solution of 4-(4-ethylpiperazin-1-yl)-6-(4-formylphenyl)thieno[3,2-c]pyridine (0.20 g) in tetrahydrofuran (20 ml) was added 3M ethylmagnesium bromide/diethyl ether solution (0.5 ml), and the mixture was reacted at room temperature for 30 min. To the resulting reaction solution was added an aqueous solution of ammonium chloride, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried. The resulting product was filtered through NH silica gel and washed with ethyl acetate. The filtrate was concentrated, to give 0.17 g of the title compound as white crystals.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.96(t,J=7.2Hz,3H), 1.17(t,J=7.2Hz,3H), 1.74-1.90(m,2H), 2.54(q,J=7.2Hz,2H), 2.70(m,4H), 3.71(m,4H), 4.64(m,1H), 7.34(d,J=5.6Hz,1H), 7.39-7.45(m,3H), 7.79(s,1H), 8.07(d,J=8.0Hz,2H).

The free compound was converted into an oxalate in a conventional manner, to give 0.16 g of the title compound as a white powder.

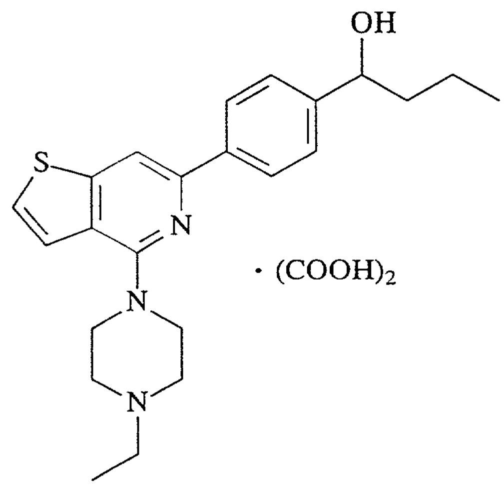
Oxalate:

m.p.; 130-131°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.84(t,J=7.2Hz,3H), 1.23(d,J=6.0Hz,3H), 1.59-1.70(m,2H), 3.07(q,J=7.2Hz,2H), 3.27(m,4H), 3.78(m,4H), 4.48(t,J=6.4Hz,1H), 7.40(d,J=8.4Hz,2H), 7.62 (d,J=5.6Hz,1H), 7.78(d,J=5.6Hz,1H), 8.09(d,J=8.4Hz,2H), 8.12(s,1H).

MS(ESI) m/z 382$(M+H)^+$.

Example 283 Synthesis of 4-(4-ethylpiperazin-1-yl)-6-[4-(1-hydroxybutyl)phenyl]thieno[3,2-c]pyridine oxalate



To a solution of 4-(4-ethylpiperazin-1-yl)-6-(4-formylphenyl)thieno[3,2-c]pyridine (0.20 g) obtained in Example 282-2 in tetrahydrofuran (20 ml) was added 2M n-propylmagnesium bromide/diethyl ether solution (1.0 ml), and the mixture was reacted at room temperature for 30 min. To the resulting reaction solution was added an aqueous solution of ammonium chloride, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried and filtered through NH silica gel, followed by washing with ethyl acetate. The resulting filtrate was concentrated, to give 0.16 g of the title compound as a white solid.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.95(t,J=7.2Hz,3H),
1.16(d,J=6.0Hz,3H), 1.28-1.53(m,2H), 1.63-1.89(m,2H),
2.53(q,J=7.2Hz,2H), 2.70(m,4H), 3.71(m,4H),

4.76(m,J=6.4Hz,1H), 7.34(d,J=5.6Hz,1H), 7.39-7.45(m,2H), 7.78(s,1H), 8.07(d,J=8.0Hz,2H).

The resulting free compound was converted into an oxalate in a conventional manner, to give the title compound (0.14 g) as a white powder.

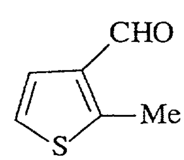
Oxalate:

m.p.; 135-136°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.85(t,J=7.2Hz,3H), 1.22(t,J=7.2Hz,3H), 1.20-1.68(m,4H), 3.11(m,2H), 3.26(m,4H), 3.77(m,4H), 4.57(m,1H), 7.39(d,J=8.4Hz,2H), 7.63(d,J=5.6Hz,1H), 7.79(d,J=5.6Hz,1H), 8.07(d,J=8.4Hz,2H), 8.19(s,1H).

Example 284 Synthesis of 4-(1-ethylpiperazin-4-yl)-6-[3-(2-hydroxyethoxy)phenyl]thieno[3,2-c]pyridine dihydrochloride

(284-1) 2-Methyl-3-thiophenecarboxaldehyde

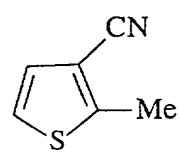


2-(Thiophen-3-yl)-1,3-dioxolane (5.076 g) was dissolved in tetrahydrofuran (50 ml), to which was then added 2.5M n-butyl lithium/hexane solution (13 ml) at -20°C in nitrogen atmosphere, and the mixture was stirred for 1.5 hr. Subsequently, methyl iodide (2.6 ml) was added to the resulting reaction mixture at -70°C, and the mixture was stirred for 30 min. After the cooling bath was removed, subsequently, the mixture was stirred at room temperature overnight. The

reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was dissolved in tetrahydrofuran (30 ml), followed by the addition of 1N hydrochloric acid (30 ml), and the mixture was stirred for 1 hr at room temperature. The resulting product was extracted with ethyl acetate, and the organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound (3.258 g, yield; 81%) as a pale yellow oil.

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 2.79(3H,s), 7.07(1H,d,J=5.4Hz), 7.38(1H,d,J=5.4Hz), 10.04(1H,s).

(284-2) 2-Methyl-3-cyanothiophene

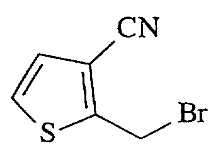


2-Methyl-3-thiophenecarboxaldehyde (3.258 g) was dissolved in ethanol (50 ml), followed by the addition of an aqueous solution (25 ml) of hydroxylamine hydrochloride (2.515 g) and sodium acetate (4.266 g), and the mixture was then stirred at 70°C for 25 min. The reaction mixture was evaporated, and the resulting residue was partitioned between ethyl acetate and water. The organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was dissolved in methylene chloride (20 ml), followed by the addition of

triethylamine (8 ml) and subsequent dropwise addition of trifluoromethanesulfonic anhydride (6 ml) under stirring at -70°C in nitrogen atmosphere. An aqueous solution of saturated sodium bicarbonate was added to the reaction mixture and extracted with chloroform. The organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a brown oil (2.108 g, yield; 65%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 2.67(3H,s), 7.11(1H,d,J=5.4Hz), 7.14(1H,d,J=5.4Hz).

(284-3) 2-Bromomethyl-3-cyanothiophene

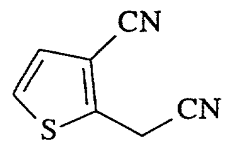


2-Methyl-3-cyanothiophene (2.108 g) was dissolved in benzene (30 ml), followed by the addition of N-bromosuccinimide (4.8 g) and 70% benzoyl peroxide (202 mg), and the mixture was stirred at 80°C for 2 hr. The reaction mixture was cooled, and the resulting precipitates were filtered off. Then the filtrate was diluted with ethyl acetate, washed with an aqueous solution of saturated sodium bicarbonate, dried (over $MgSO_4$) and then evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a yellow oil (2.746 g, yield; 82%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 4.80(2H,s), 7.18(1H,d,J=5.4Hz),

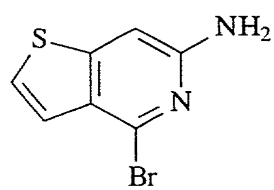
7.39(1H,d,J=5.4Hz).

(284-4) 2-Cyanomethyl-3-cyanothiophene



2-Bromomethyl-3-cyanothiophene (2.746 g) was dissolved in toluene (40 ml), followed by the addition of a solution of sodium cyanide (2.002 g)/water (15 ml), and the mixture was stirred at 80°C overnight. The reaction mixture was diluted with ethyl acetate and washed with an aqueous solution of saturated sodium bicarbonate, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a pale yellow solid (823 mg, yield; 43%).
^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 4.13(2H,s), 7.23(1H,d,J=5.2Hz), 7.41(1H,d,J=5.2Hz).

(284-5) 6-Amino-4-bromothieno[3,2-c]pyridine

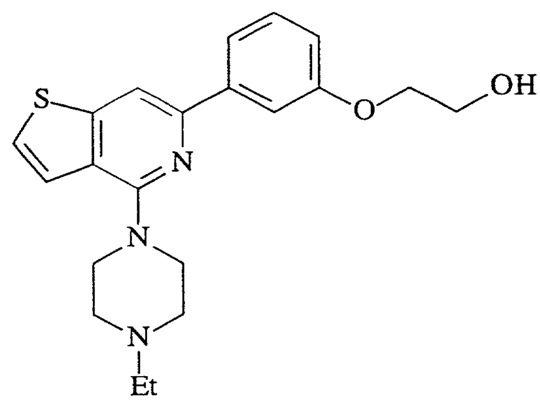


2-Cyanomethyl-3-cyanothiophene (823 mg) was added to a solution (30 ml) of 25 % hydrogen bromide in acetic acid, and the resulting mixture was stirred under ice-cooling for 90 min, which was neutralized with a 8N aqueous solution of sodium hydroxide and then extracted with ethyl acetate. The organic layer was washed with water, dried (over $MgSO_4$) and evaporated.

The residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a yellow solid (894 mg, yield; 70%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 4.49(2H,br-s), 6.85(1H,d,J=0.8Hz), 7.14(1H,d,J=5.6Hz), 7.25(1H,dd,J=5.6Hz,0.8Hz).

(284-6) 4-(1-Ethylpiperazin-4-yl)-6-[3-(2-hydroxyethoxy)phenyl]thieno[3,2-c]pyridine dihydrochloride



6-Amino-4-bromothieno[3,2-c]pyridine (894 mg) was treated in the same manner as in Example 245-1, to obtain a mixture of 4,6-dibromothieno[3,2-c]pyridine and 4,6,7-tribromothieno[3,2-c]pyridine (6:4). Continuously, the mixture was treated in the same manner as in Example 245-2 and then treated with 3-tributylstannylphenoxyethyl acetate(394 mg) in the same manner as in Example 300-4. Then, the reaction mixture was dissolved in N,N-dimethylformamide (15 ml), followed by the addition of t-butyldimethylsilyl chloride (241 mg) and imidazole (136 mg), and the mixture was stirred for 1 hr at room temperature. The reaction solution was partitioned

between ethyl acetate and water. The organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The residue was dissolved in tetrahydrofuran (12 ml), followed by the addition of 2.5M n-butyl lithium/hexane solution (480 ml) in nitrogen atmosphere at -70°C, and the mixture was stirred for 30 min. Then, an aqueous solution of saturated ammonium chloride was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The residue was purified by (NH) silica gel column chromatography (ethyl acetate/hexane system). The resulting product was then converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as a colorless amorphous (288 mg, yield; 15%).

Hydrochloride:

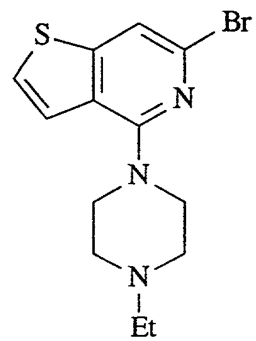
m.p.; 126-130°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.29(3H,t,J=7.2Hz), 3.13-3.27(4H,m), 3.47-3.62(4H,m), 3.74(2H,t,J=5Hz), 4.07(2H,t,J=5Hz), 4.20(2H,d,J=13.6Hz), 6.96(1H,dd,J=8.2Hz,2.4Hz), 7.37(1H,t,J=8.2Hz), 7.63(1H,d,J=5.6Hz), 7.70(1H,d,J=2.4Hz), 7.71(1H,d,J=8.4Hz), 7.83(1H,d,J=5.6Hz), 8.28(1H,s), 11.00-11.10(1H,br-s).

ESI-Mass; 384(MH^+).

Example 285 Synthesis of 4-(1-ethylpiperazin-4-yl)-6-[4-(3-hydroxybutyl)phenyl]thieno[3,2-c]pyridine hydrochloride

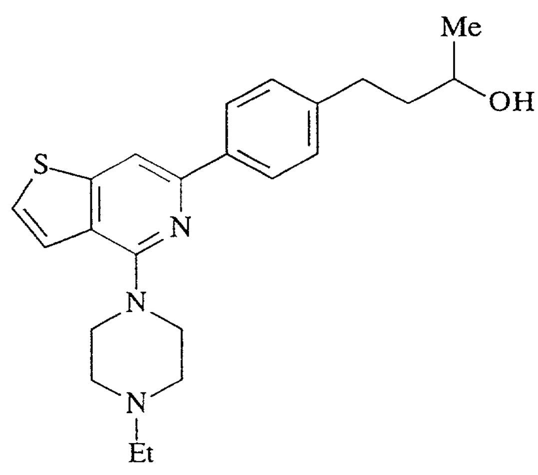
(285-1) 4-(1-Ethylpiperazin-4-yl)-6-bromothieno[3,2-c]pyridine



2-Cyanomethylthiophene-3-carboxylic acid (2.331 g) was treated in the same manner as in Example 300-1, to give the title compound as a yellow oil (183 mg, yield; 4%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.14(3H,t,J=7.2Hz), 2.50(2H,q,J=7.2Hz), 2.63(4H,t,J=5Hz), 3.66(4H,t,J=5Hz), 7.30(1H,d,J=5.6Hz), 7.35(1H,d,J=5.6Hz,0.8Hz), 7.43(1H,d,J=0.8Hz).

(285-2) 4-(1-Ethylpiperazin-4-yl)-6-[4-(3-hydroxybutyl)phenyl]thieno[3,2-c]pyridine hydrochloride



In the same manner as in Example 167-3, the hydrochloride of the title compound was obtained as a pale yellow amorphous (98 mg, yield; 33%) from 4-[3-(t-

butyldimethylsilyloxy)butyl)-1-bromobenzene (889 mg) and 4-(1-ethylpiperazin-4-yl)-6-bromothieno[3,2-c]pyridine (183 mg).

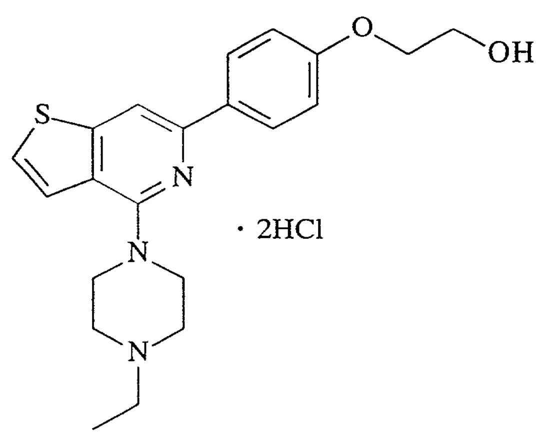
Hydrochloride:

m.p.; 122-124°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.08(3H,d,J=6.4Hz), 1.29(3H,t,J=7.2Hz), 1.58-1.66(2H,m), 2.57-2.74(2H,m), 3.14-3.25(4H,m), 3.49-3.62(5H,m), 4.19(2H,d,J=8.8Hz), 7.61(1H,d,J=5.2Hz), 7.80(1H,d,J=5.2Hz), 8.03(2H,d,J=8.8Hz), 8.2(1H,s), 11.00-11.10(1H,br-s).

ESI-Mass; 396(MH$^+$).

Example 286 Synthesis of 4-(1-ethylpiperazin-4-yl)-6-[4-(3-hydroxybutyl)phenyl]thieno[3,2-c]pyridine dihydrochloride



4-(4-Ethylpiperazin-1-yl)-6-(4-hydroxyphenyl)thieno[3,2-c]pyridine (1.01 g) obtained in Example 289-7 was dissolved in DMF (4 ml), followed by the addition of 60% sodium hydride (0.16 g). After the evolution of hydrogen was ceased, 2-(t-butyldimethylsilyloxy)ethyl bromide (1.43 g) was added thereto, and the mixture was stirred

at 50°C overnight. The reaction solution was partitioned between ethyl acetate and water. The organic layer was washed with water, dried and evaporated. The resulting residue was dissolved in THF (10 ml), followed by the addition of 1.0M tetra(n-butyl)ammonium fluoride/THF solution (1.75 ml), and the mixture was stirred at room temperature for 30 min. The solvent was evaporated, and the resulting residue was partitioned between ethyl acetate and water. The resulting product was extracted from the organic layer with 2N hydrochloric acid. The aqueous layer was basified with 2N sodium hydroxide, which was then back-extracted with ethyl acetate. The organic layer was washed with water, dried and evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system) and NH-silica gel column chromatography (ethyl acetate), to give 0.475 g of the free compound of the title compound as a colorless oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 2.09(br-s,1H), 2.53(q,J=7.2Hz,2H), 2.70(t,J=4.8Hz,4H), 3.70(t,J=4.8Hz,4H), 4.00(br-t,2H), 4.15(t,J=4.4Hz,2H), 7.00(d,J=9.0Hz,2H), 7.32(d,J=5.6Hz,1H), 7.39(dd,J=0.8,5.6Hz,1H), 7.72(d,J=0.8Hz,1H), 8.05(d,J=9.0Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, to give 0.565 g of the

title compound as a pale yellow powder.

Hydrochloride:

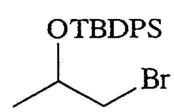
m.p.; 128-129°C

^{1}H-NMR(400MHz, DMSO-d_6); δ (ppm) 1.31(t, J=7.2Hz, 3H), 3.18-3.28(m, 4H), 3.50(br-t, 2H), 3.60(br-d, 2H), 3.75(t, J=5.1Hz, 2H), 4.05(t, J=5.1Hz, 2H), 4.22(br-d, 2H), 7.05(d, J=8.8Hz, 2H), 7.62(d, J=7.2Hz, 1H), 7.79(d, J=5.6Hz, 1H), 8.10(d, J=8.8Hz, 2H), 8.18(s, 1H), 10.76(br-s, 1H).

MS(ESI) m/z 384(M+H)$^+$.

Example 287 Synthesis of 4-(4-ethylpiperazin-1-yl)-6-[4-(2-hydroxypropoxy)phenyl]thieno[3,2-c]pyridine

(287-1) 1-Bromo-O-(t-butyl)diphenylsilyl-2-propanol



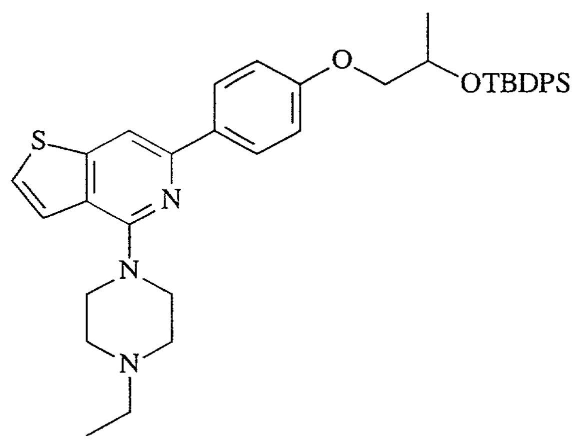
(In the formula, TBDPS represents (t-butyl)diphenylsilyl group.)

A solution of 2-(t-butyl)diphenylsilyloxypropanol of 5.27 g (16.8 mmol) synthetically prepared according to *J. Am. Chem. Soc.*, 1985, 107, 5556, triphenylphosphine of 4.40 g (1.0 equivalent), pyridine of 2.03 ml (1.5 equivalents) and dry THF (50 ml) was stirred under ice-cooling. To the resulting mixture was added dropwise bromide (0.864 ml, 1.0 equivalent), and the mixture was further stirred for 50 min. Ethyl acetate and water were added thereto, and the resulting mixture was stirred. The organic layer was separated, then, it was washed sequentially with an aqueous solution of sodium thiosulfate, water and brine,

and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (n-hexane/ethyl acetate system). n-Hexane was added to the resulting product to dissolve the product, and the resulting insoluble matters were filtered off. The solvent was evaporated, to give the title compound as a colorless oil (5.706 g, yield; 90%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.07(s, 9H), 1.22(d,J=6.0Hz,3H), 3.25(dd,J=6.4,10.0Hz), 3.31(dd,J=4.4,10.0Hz), 3.96-4.03(m,1H), 7.36-7.46(m,6H), 7.66-7.71(m,4H).

(287-2) 4-(4-Ethylpiperazin-1-yl)-6-[4-(2-t-butyldiphenylsilyloxypropoxy)phenyl]thieno[3,2-c]pyridine

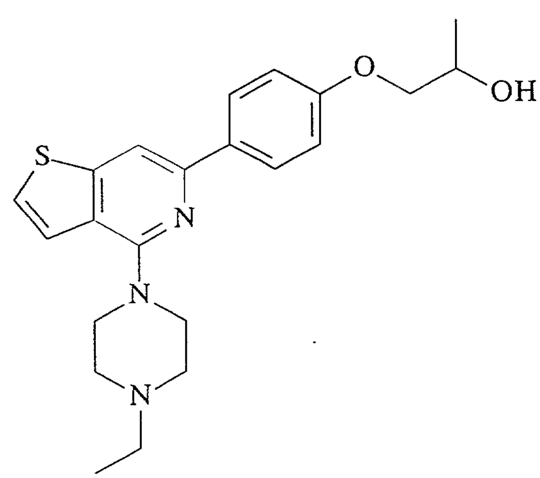


66% sodium hydride (0.26 g, 1.2 equivalents) was washed with n-hexane and was then suspended in DMF of 1 ml, and the mixture was stirred under ice-cooling. To the resulting mixture was added 4-(4-ethylpiperazin-1-yl)-6-(4-hydroxyphenyl)thieno[3,2-c]pyridine of 2.00 g (5.88 mmol) dissolved in DMF of 20 ml, followed by the agitation at room temperature for 45 min. To the resulting product was added

1-bromo-O-(t-butyl)diphenylsilyl-2-propanol of 4.44 g (2.0 equivalents) dissolved in DMF of 15 ml, which was stirred in nitrogen atmosphere at 50°C for 18 hr. Water was added to the resulting mixture, and then extracted with ethyl acetate. The organic layer was washed sequentially with water (three times) and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by NH-silica gel column chromatography (eluent solvent/ethyl acetate system), to give the title compound as a pale yellow oil (3.38 mg, yield; 90%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.08(s,9H), 1.16(t,J=7.2Hz,3H), 1.21(d,J=6.4Hz,3H), 2.53(q,J=7.2Hz,2H), 2.70(t,J=4.8Hz,4H), 3.70(t,J=4.8Hz,4H), 3.81(dd,J=5.4,9.2Hz,1H), 3.97(dd,J=6.0,9.2Hz,1H), 4.17-4.24(m,1H), 7.80(d,J=8.8Hz,2H), 7.31(d,J=5.6Hz,1H), 7.34-7.45(m,7H), 7.70-7.74(m,5H), 7.97(d,J=8.8Hz,2H).

<u>(287-3) 4-(4-Ethylpiperazin-1-yl)-6-[4-(2-hydroxypropoxy)phenyl]thieno[3,2-c]pyridine</u>



4-(4-Ethylpiperazin-1-yl)-6-[4-(2-t-butyldiphenylsilyloxypropoxy)phenyl]thieno[3,2-c]pyridine of 3.38 g (5.31 mmol) was dissolved in THF of 20 ml and stirred at room temperature. To the mixture was added 1.0M tetrabutylammonium fluoride/THF solution of 10.6 ml (2.0 equivalents), and the mixture was stirred for 8 hr. The solvent was evaporated, and to the resulting residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed sequentially with water (three times) and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by NH-silica gel column chromatography (n-hexane/ethyl acetate system), to give the title compound as a colorless oil (1.65 g, yield; 78%).

The resulting compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/diisopropyl ether/water, to give 1.91 g of the hydrochloride of the title compound as a pale yellow powder.

Hydrochloride:

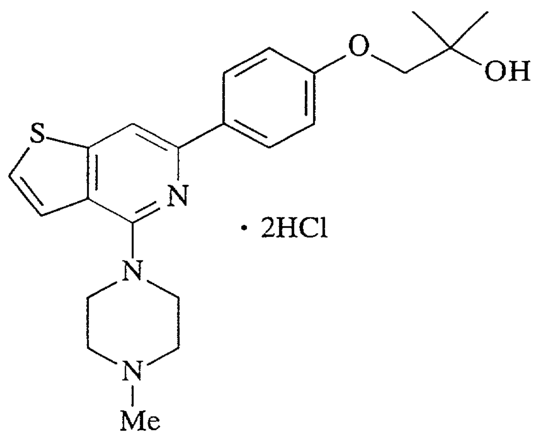
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.17(d,J=7.2Hz,3H), 1.31(t,J=7.2Hz,3H), 3.18-3.28(m,4H), 3.49(br-t,2H), 3.60(br-d,2H), 3.83-3.91(m,2H), 3.94-4.01(m,1H), 4.21(br-d,2H), 7.04(d,J=9.2Hz,2H), 7.62(d,J=5.6Hz,1H), 7.79(d,J=5.6Hz,1H), 8.07-8.11(m,3H), 8.18(s,1 H), 10.72(br-s,1H).

MS(FAB) m/z 398(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 1.31(d,J=6.4Hz,3H), 2.53(q,J=7.2Hz,2H), 2.70(t,J=4.8Hz,4H), 3.70(t,J=4.8Hz,4H), 3.86(dd,J=8.0,9.2Hz,1H), 4.01(dd,J=3.0,9.2Hz,1H), 4.20-4.27(m,1H), 6.99(d,J=8.8Hz,2H), 7.32(d,J=5.4Hz,1H), 7.39(dd,J=0.4,5.4Hz,1H), 7.72(d,J=7.2Hz,1H), 8.05(d,J=8.8Hz,2H).

Example 288 Synthesis of 6-[4-(2-methyl-2-hydroxypropoxy)phenyl]-4-(4-methylpiperazin-1-yl)thieno[3,2-c]pyridine hydrochloride



4-(4-Methylpiperazin-1-yl)-6-(4-hydroxyphenyl)thieno[3,2-c]pyridine (543 mg) was dissolved in DMF (20 ml), followed by the addition of 60% sodium hydride (87 mg). The mixture was stirred at room temperature for 30 min, to which was then added ethyl bromoacetate (0.185 ml) at 0 °C, and the mixture was stirred for 15 min. The reaction solution was partitioned between ethyl acetate and water. The organic layer was washed with water, dried and evaporated. The resulting residue was dissolved in THF (30 ml), followed by the addition of 3.0M methylmagnesium bromide/ether solution (3.3

ml) under ice-cooling, and the mixture was reacted at room temperature for 1.5 hr. The reaction solution was partitioned between ethyl acetate and water. The organic layer was washed with water, dried and evaporated. The resulting residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate system), to give a colorless oil (209 mg, yield; 31%).

The resulting oil was converted into a hydrochloride in a conventional manner, to give the title compound as yellow crystals.

Hydrochloride:

m.p.; 135-138°C

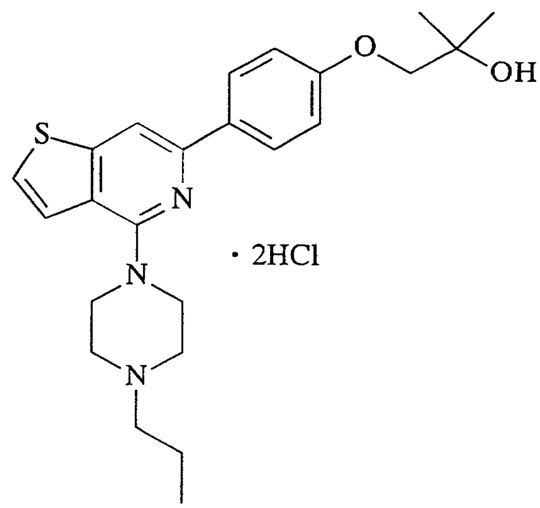
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.23(s,6H), 2.86(d,J=4.8Hz,3H), 3.25-3.33(m,2H), 3.45(t,J=13.2Hz,2H), 3.54(d,J=11.2Hz,2H), 3.78(s,2H), 4.21(d,J=14.0Hz,2H), 7.04(d,J=8.8Hz,2H), 7.61(d,J=5.6Hz,1H), 7.78(d,J=5.6Hz,1H), 8.09(d,J=8.8Hz,2H), 8.18(s,1H).

MS(FAB) m/z 398$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.37(s,6H), 2.39(s,3H), 2.66(t,J=4.8Hz,4H), 3.69(t,J=4.8Hz,4H), 3.86(s,2H), 7.00(d,J=8.8Hz,2H), 7.32(d,1H,J=5.6Hz), 7.38(d,J=5.6Hz,1H), 7.73(s,1H), 8.05(d,J=8.8Hz,2H).

Example 289 Synthesis of 6-[4-(2-methyl-2-hydroxypropoxy)phenyl]-4-(4-propylpiperazin-1-yl)thieno[3,2-c]pyridine hydrochloride



In the same manner as in Example 289, a yellow compound was obtained (240 mg, yield; 35%) from 4-(4-propylpiperazin-1-yl)-6-(4-hydroxyphenyl)thieno[3,2-c]pyridine (603 mg), ethyl bromoacetate (0.18 ml) and 3.0M methylmagnesium bromide (1.6 ml). The resulting compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 133-135°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.19(t,J=7.2Hz,3H), 1.23(s,6H), 1.70-1.81(m,2H), 3.03-3.13(m,4H), 3.20-3.30(m,2H), 3.50-3.61(m,2H), 3.78(s,2H), 4.19(d,J=12.8Hz,2H), 7.04(d,J=8.8Hz,2H), 7.61(d,J=5.6Hz,1H), 7.78(d,J=5.6Hz,1H), 8.10(d,J=8.8Hz,2H), 8.18(s,1H).

MS(FAB) m/z 426(M+H)$^+$.

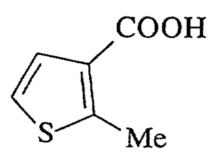
Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.95(t,J=7.6Hz,3H), 1.37(s,6H), 1.56-1.61(m,2H), 2.38-2.43(m,2H), 2.68(t,J=5.2Hz,4H),

3.69(t,J=5.2Hz,4H), 3.86(s,2H), 7.00(d,J=8.8Hz,2H), 7.31(d,J=5.6Hz,1H), 7.39(d,J=5.6Hz,1H), 7.72(s,1H), 8.05(d,J=8.8Hz,2H).

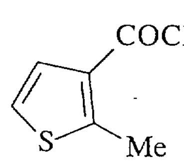
Example 290 Synthesis of 6-[4-(2-methyl-2-hydroxypropoxy)phenyl]-4-(4-ethylpiperazin-1-yl)thieno[3,2-c]pyridine dihydrochloride

(290-1) 2-Methyl-3-thiophenecarboxylic acid



To a solution of 1.5M-lithium diisopropylamide/cyclohexane solution (600 ml) and THF (300 ml) was dropwise added 3-thiophenecarboxylic acid (50.0 g)/THF (150 ml) under vigorous stirring at -70°C. After the reaction mixture was stirred, as it was, at -70 °C for 2 hr, methyl iodide (60.0 g) was added dropwise to the reaction mixture. After the dry ice/acetone bath was removed, the mixture was reacted overnight. The resulting reaction solution was acidified by adding 5N hydrochloric acid thereto, and then extracted with ethyl acetate. The organic layer was washed with water and brine, dried and evaporated, to give 54 g of the title compound.

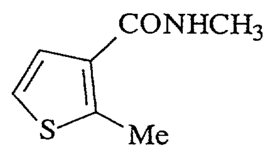
(290-2) 2-Methyl-3-thiophenecarboxylate chloride



2-Methyl-3-thiophenecarboxylic acid (54 g) was reacted

with thionyl chloride (100 ml) at 60°C for 1.5 hr. The reaction solution was evaporated, and to the resulting residue was added THF (100 ml×2), and then excess thionyl chloride was removed, to give 60.5 g of the title compound.

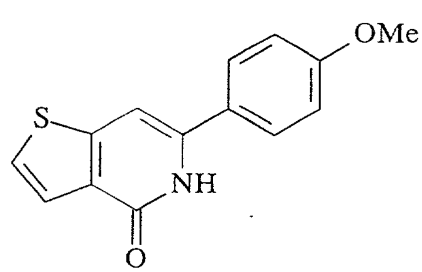
(290-3) N-Methyl-2-methylthiophene-3-carboxamide



2-Methyl-3-thiophenecarboxylate chloride (60.5 g)/THF (300 ml) solution was added dropwise to a 40% aqueous solution of methylamine (400 ml) at 0 °C. Ethyl acetate (2 l) was added thereto, and then the organic layer was washed sequentially with water, a 5N aqueous solution of hydrochloric acid, an aqueous solution of saturated sodium bicarbonate, water and brine, dried and evaporated. The resulting residue was crystallized from n-hexane, to give the title compound as a white powder (43.5 g, yield; 71.8%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 2.70(3H,s), 2.96(3H,d,J=7.2Hz), 5.82(1H,br), 7.03(1H,d,J=5.2Hz), 7.08(1H,d,J=5.2Hz).

(290-4) 6-(4-Methoxyphenyl)-5H-thieno[3,2-c]pyridin-4-one

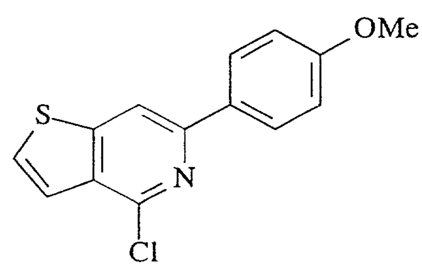


To a solution of N-methyl-2-methylthiophene-3-

carboxamide (36.0 g) in THF (500 ml) was added dropwise 2.5M n-BuLi/THF solution (200 ml) at -70 °C. The reaction solution was stirred at -70°C for 2 hr, followed by the addition of anisonitrile (31.0 g) at once. After the dry ice/acetone bath was removed, the reaction mixture was back to room temperature. Three hours later, an aqueous solution of saturated ammonium chloride and ether were added thereto, and then the mixture was further stirred for 1 hr. The resulting white precipitates were collected by filtration, washed with water, ether and n-hexane in this order, and then dried, to give the title compound (17.9 g, yield; 30%).

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 3.81(3H,s), 7.04(2H,d,J=8.4Hz), 7.15(1H,s), 7.47(1H,d,J=5.2Hz), 7.56(1H,d,J=5.2Hz), 7.73(2H,d,J=8.4Hz).

(290-5) 4-Chloro-6-(4-methoxyphenyl)thieno[3,2-c]pyridine

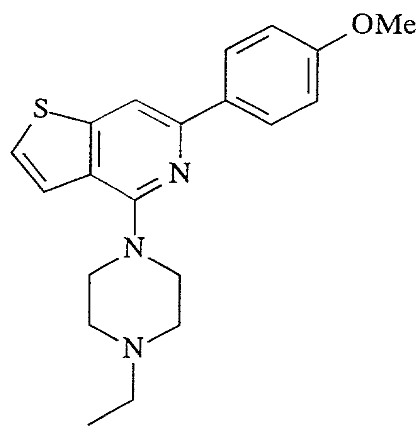


6-(4-Methoxyphenyl)-5H-thieno[3,2-c]pyridin-4-one (9.1 g) was added to phosphorus oxychloride (90 g), and the mixture was heated at 120°C for 3 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water. The organic layer was washed with water, an aqueous solution of saturated sodium bicarbonate and brine,

and dried over magnesium sulfate. The solvent was evaporate, and the resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a white powder (6.6 g, yield; 73%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 3.86(3H,s), 7.01(2H,d,J=8.8Hz), 7.50(2H,m), 8.01(2H,d,J=8.8Hz), 8.06(1H,s).

(290-6) 4-(4-Ethylpiperazin-1-yl)-6-(4-methoxyphenyl)thieno[3,2-c]pyridine

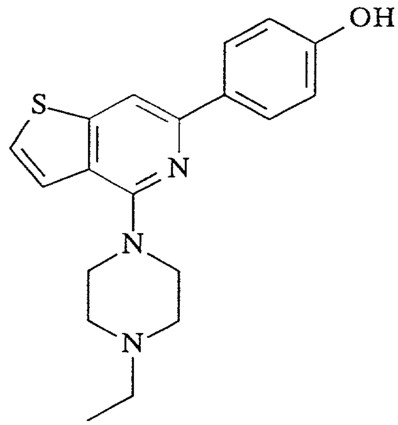


A mixture of 4-chloro-6-(4-methoxyphenyl)thieno[3,2-c]pyridine (6.6 g) and N-ethylpiperazine (30 ml) was heated at 130°C for 2 hr. The reaction mixture was evaporated, and to the resulting residue were added potassium carbonate and water. The resulting mixture was extracted with ethyl acetate, and the resulting organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was removed, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the title compound as a pale brown oil (5.2 g, yield; 61.5%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(3H,t,J=7.2Hz),

2.55(2H,q,J=7.2Hz), 2.72(4H,br), 3.71(4H,br), 6.99(2H,d,J=8.8Hz), 7.32(1H,d,J=6.0Hz), 7.38(1H,dd,J=6.0,0.8Hz), 7.73(1H,d,J=0.8Hz), 8.05(2H,d,J=8.8Hz).

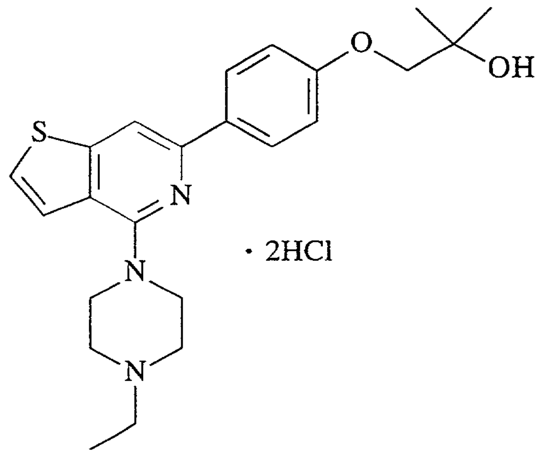
(290-7) 4-(4-Ethylpiperazin-1-yl)-6-(4-hydroxyphenyl)thieno[3,2-c]pyridine



4-(4-Ethylpiperazin-1-yl)-6-(4-methoxyphenyl)thieno[3,2-c]pyridine (5.2 g) was dissolved in 48% hydrobromic acid (50 ml), and the mixture was reacted at 130°C for 1.5 hr. The reaction solution was evaporated, basified with potassium carbonate and extracted with chloroform. The chloroform layer was washed with water, dried and evaporated. The resulting residue was purified by NH-silica gel column chromatography (ethyl acetate), to give the title compound as a pale brown powder (4.0 g, yield; 80%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.21(3H,t,J=7.2Hz), 2.62(2H,q,J=7.2Hz), 7.82(4H,br), 3.76(4H,br), 6,92(2H,d,J=8.4Hz), 7.33(1H,d,J=5.6Hz), 7.37(1H,d,J=5.6Hz), 7.73(1H,s), 7.99(2H,d,J=8.4Hz).

(290-8) 6-[4-(2-Methyl-2-hydroxy)propoxyphenyl]-(4-ethylpiperazin-1-yl)thieno[3,2-c]pyridine hydrochloride hydrochloride



4-(4-Ethylpiprazin-1-yl)-6-(4-hydroxyphenyl)thieno[3,2-c]pyridine (1.10 g) was dissolved in DMF (30 ml), followed by the addition of 60% sodium hydride (0.18 g). After the evolution of hydrogen was ceased, ethyl bromoacetate (0.55 g) was added thereto, which was then stirred at 0°C for 30 min. The reaction solution was partitioned between ethyl acetate and water. The organic layer was washed with water, dried and evaporated. The resulting residue was dissolved in THF (30 ml), followed by the addition of 3M methylmagnesium bromide/ether solution (3.3 ml) under ice-cooling, and the mixture was reacted at room temperature for 1.5 hr. The reaction solution was partitioned between ethyl acetate and water, and the aqueous layer was extracted from the organic layer with 2N hydrochloric acid. The aqueous layer was basified with 2N sodium hydroxide and back-extracted with ethyl

acetate. The organic layer was washed with water, dried and evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system) and NH-silica gel chromatography (ethyl acetate), to give the free compound of the title compound as a colorless oil (0.71 g, yield; 53.2%).

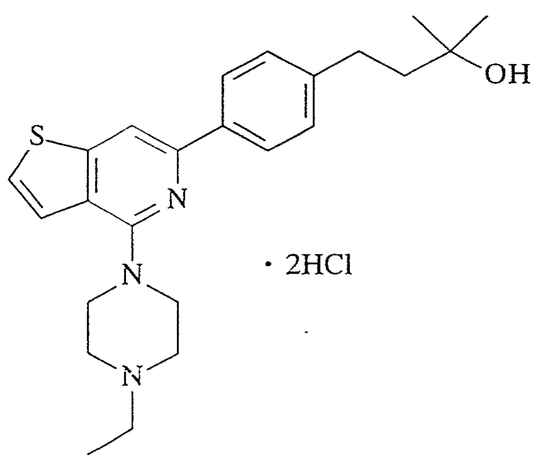
The resulting oil was converted into a hydrochloride in a conventional manner, to give 0.72 g of the title compound as a pale yellow powder.

Hydrochloride:

3.28(m,2H), 3.40(q,J=7.2Hz,2H), 3.50(br-t,2H), 3.62(br-d,2H), 3.97(br-d,2H), 6.90(d,J=8.8Hz,2H), 7.55(t,J=8.0Hz,1H), 7.71(t,J=8.0Hz,1H), 7.93(s,2H), 7.91-7.96(m,1H), 8.04(d,J=8.8Hz,2H), 8.08(d,J=8.8Hz,2H), 10.92(br-s,1H).

MS(FAB) m/z 378$(M+H)^+$.

Example 291 Synthesis of 4-(4-ethylpiperazin-1-yl)-6-[4-(3-hydroxy-3-methylbutyl)phenyl]thieno[3,2-c]pyridine dihydrochloride



6-(4-Bromophenyl)-4-(4-ethylpiperazin-1-yl)thieno[3,2-c]pyridine (1.265 g) and 2-methyl-3-butyn-2-ol (915 μl) were heated under reflux in the presence of bistriphenylphosphine dichloride (44 mg), triphenylphosphine (165 mg) and cuprous iodide (22 mg) in DMF (12 ml) and triethylamine (20 ml) for 1.5 hr. The reaction solution was evaporated, and the resulting residue was purified by NH-silica gel column chromatography (ethyl acetate/hexane system), to give 6-[4-(3-methyl-3-hydroxy-1-butynyl)phenyl]-(4-ethylpiperazin-1-yl)thieno[3,2-c]pyridine (0.414 g) as a pale yellow oil.

6-[4-(3-Methyl-3-hydroxy-1-butynyl)phenyl]-(4-ethylpiperazin-1-yl)thieno[3,2-c]pyridine (0.299 g) was dissolved in a mixture solution of benzene (30 ml)/THF (15 ml), and the hydrogenation reaction was conducted with a catalyst of chlorotristriphenylphosphinerhodium. The reaction solution was filtered and washed with methanol, and the resulting filtrate was concentrated. The resulting residue was purified by NH-silica gel column chromatography (ethyl acetate/hexane system), to give 0.097 g of 4-(4-ethylpiperazin-1-yl)-6-[4-(3-hydroxy-3-methylbutyl)phenyl)thieno[3,2-c]pyridine of as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 1.31(s,6H), 1.81-1.85(m,2H), 2.52(q,J=7.2Hz,2H), 2.69(t,J=5.0Hz,4H),

2.73-2.77(m,2H), 3.70(t,J=5.0Hz,4H), 7.28(d,J=8.4Hz,2H), 7.32(d,J=5.6Hz,1H), 7.39(dd,J=0.8,5.6Hz,1H), 7.76(d,J=0.8Hz,1H), 8.01(d,J=8.4Hz,2H).

The resulting oil was converted into a hydrochloride in a conventional manner, to give the title compound (0.72 g) as a pale yellow powder.

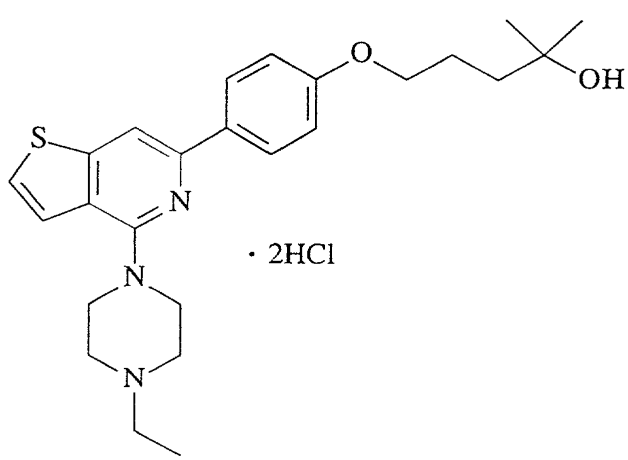
Hydrochloride:

m.p.; 116-117.5°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.16(s,6H), 1.31(t,J=7.2Hz,3H), 1.65-1.69(m,2H), 2.65-2.69(m,2H), 3.17-3.28(m,4H), 3.51(br-t,2H), 3.60(br-d,2H), 4.22(br-d,2H), 7.30(d,J=8.4Hz,2H), 7.63(d,J=5.6Hz,1H), 7.82(d,J=5.6Hz,1H), 8.06(d,J=8.4Hz,2H), 8.22(s,1H), 10.80(br-s,1H).

MS(FAB) m/z 410(M+H)$^+$.

Example 292 Synthesis of 6-[4-(4-methyl-4-hydroxypentyloxy)phenyl]-4-(4-ethylpiperazin-1-yl)thieno[3,2-c]pyridine



In the same manner as in Example 289, a yellow compound

was obtained (359 mg, yield; 55%) from 4-(4-ethylpiperazin-1-yl)-6-(4-hydroxyphenyl)thieno[3,2-c]pyridine (816 mg), ethyl-4-bromobutyrate (0.42 ml) and 3.0M methylmagnesium bromide/THF solution (1.3 ml). The resulting compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 116-118°C

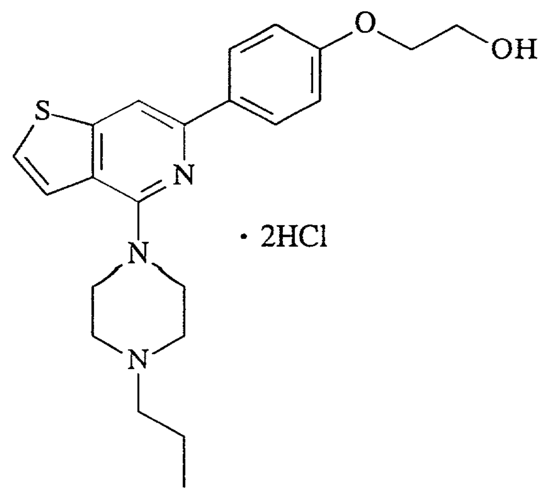
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.12(s,6H), 1.30(t,J=7.2Hz,3H), 1.48-1.52(m,2H), 1.74-1.82(m,2H), 3.17-3.28(m,4H), 3.48(t,J=12.0Hz,2H), 3.58-3.62(m,2H), 4.02(t,J=5.6Hz,2H), 4.02(d,J=14.0Hz,2H), 7.02(d,J=8.8Hz,2H), 7.61(d,J=5.6Hz,1H), 7.78(d,J=5.6Hz,1H), 8.09(d,J=8.8Hz,2H), 8.17(s,1H).

MS(FAB) m/z 440(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.6Hz,3H), 1.27(s,6H), 1.65-1.69(m,2H), 1.89-1.94(m,2H), 2.52(q,J=7.6Hz,2H), 2.69(t,J=4.8Hz,4H), 3.69(t,J=4.8Hz,4H), 4.05(t,J=6.4Hz,2H), 6.97(d,J=8.4Hz,2H), 7.31(d,J=5.6Hz,1H), 7.39(d,J=5.6Hz,1H), 7.71(s,1H), 8.03(d,J=8.4Hz,2H).

Example 293 Synthesis of 4-(4-propylpiperazin-1-yl)-6-[4-(2-hydroxyethoxy)phenyl]thieno[3,2-c]pyridine



In the same manner as in Example 289, a yellow compound was obtained (310 mg, yield; 82%) from 4-(4-propylpiperazin-1-yl)-6-(4-hydroxyphenyl)thieno[3,2-c]pyridine (603 mg) and 2-bromoethanol (0.24 ml). The resulting compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 128-130°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.20(t,J=7.2Hz,3H), 1.76-2.09(m,2H), 3.02-3.12(m,2H), 3.23-3.29(m,2H), 3.59-3.62(m,4H), 3.75(t,J=4.8Hz,2H), 4.05(t,J=4.8Hz,2H), 4.19(d,J=13.6Hz,2H), 7.04(d,J=8.8Hz,2H), 7.61(d,J=5.6Hz,1H), 7.78(d,J=5.6Hz,1H), 8.10(d,J=8.8Hz,2H), 8.18(s,1H).

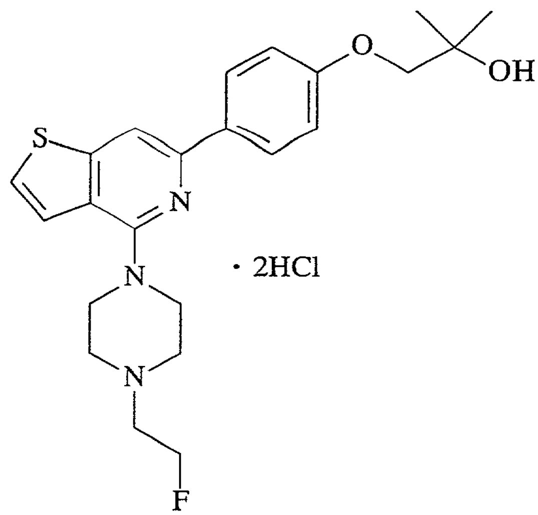
MS(FAB) m/z 398(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.95(t,J=7.6Hz,3H), 1.56-1.62(m,2H), 2.39-2.43(m,2H), 2.68(t,J=5.2Hz,4H),

3.68(t,J=4.8Hz,4H), 4.00(br-t,2H), 4.15(t,J=4.8Hz,2H), 7.00(d,J=8.8Hz,2H), 7.32(d,J=5.6Hz,1H), 7.39(d,J=5.6Hz,1H), 7.72(s,1H), 8.05(d,J=8.8Hz,2H).

Example 294 Synthesis of 6-[4-(2-methyl-2-hydroxypropoxy)phenyl]-4-[4-(2-fluoroethyl)piperazin-1-yl]thieno[3,2-c]pyridine



In the same manner as in Example 289, a yellow compound was obtained (245 mg, yield; 34%) from 4-[4-(2-fluoroethyl)piperazin-1-yl]-6-(4-hydroxyphenyl)thieno[3,2-c]pyridine (600 mg), ethyl bromoacetate (0.18 ml) and 3.0M methylmagnesium bromide (1.7 ml). The resulting compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 135-137°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.23(s,6H), 3.35-3.45(m,2H), 3.54-3.65(m,6H), 3.78(s,2H), 4.22(d,J=13.6Hz,2H),

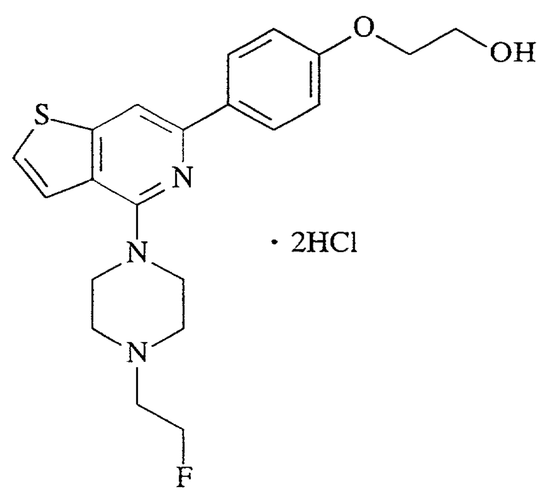
4.92(t,J=4.4Hz,1H), 5.04(t,J=4.4Hz,1H), 7.04(d,J=8.8Hz,2H), 7.63(d,J=5.6Hz,1H), 7.79(d,J=5.6Hz,1H), 8.10(d,J=8.8Hz,2H), 8.19(s,1H).

MS(FAB) m/z 430(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.37(s,6H), 2.77-2.80(m,1H), 2.79(t,J=4.8Hz,4H), 2.85(t,J=5.2Hz,1H), 3.70(t,J=4.8Hz,4H), 3.85(s,2H), 4.59(t,J=4.8Hz,1H), 4.71(t,J=4.8Hz,1H), 7.00(d,J=8.8Hz,2H), 7.32(d,J=5.6Hz,1H), 7.38(d,J=5.6Hz,1H), 7.73(s,1H), 8.04(d,J=8.8Hz,2H).

Example 295 Synthesis of 4-[4-(2-fluoroethyl)piperazin-1-yl]-6-[4-(2-hydroxyethoxy)phenyl]thieno[3,2-c]pyridine



In the same manner as in Example 289, a yellow compound was obtained (231 mg, yield; 68%) from 4-[4-(2-fluoroethyl)piperazin-1-yl]-6-(4-hydroxyphenyl)thieno[3,2-c]pyridine (300 mg) and 2-bromoethanol (0.12 ml). The resulting compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title

compound as yellow crystals.

Hydrochloride:

m.p.; 138-140°C

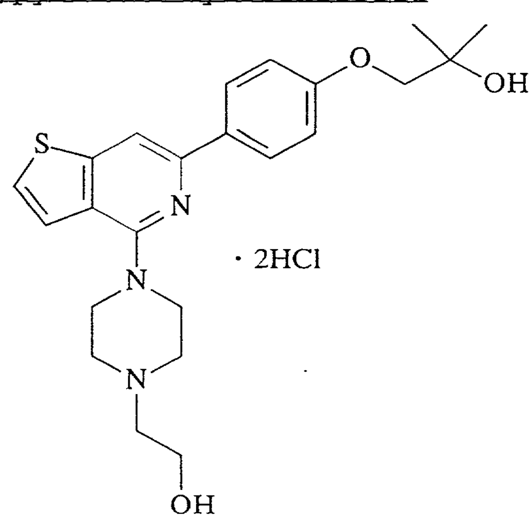
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 3.36-3.43(m,2H), 3.53-3.66(m,6H), 3.75(t,J=4.8Hz,2H), 4.05(t,J=4.8Hz,2H), 4.23(d,J=13.6Hz,2H), 4.92(t,J=4.4Hz,1H), 5.03(d,J=4.4Hz,1H), 7.05(d,J=8.8Hz,2H), 7.63(d,J=5.6Hz,1H), 7.79(d,J=5.6Hz,1H), 8.10(d,J=8.8Hz,2H), 8.19(s,1H).

MS(FAB) m/z 402(M+H)$^{+}$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 2.77-2.85(m,1H), 2.79(t,J=4.4Hz,4H), 2.85(t,J=5.2Hz,1H), 3.70(t,J=4.4Hz,4H), 3.99(brt,2H), 4.15(t,J=4.0Hz,2H), 4.59(t,J=4.8Hz,1H), 4.71(t,J=4.8Hz,1H), 7.00(d,J=8.8Hz,2H), 7.33(d,J=5.6Hz,1H), 7.39(d,J=5.6Hz,1H), 7.73(s,1H), 8.05(d,J=8.8Hz,2H).

Example 296 Synthesis of 6-[4-(2-methyl-2-hydroxypropoxy)phenyl]-4-[4-(2-hydroxyethyl)piperazin-1-yl]thieno[3,2-c]pyridine hydrochloride



In the same manner as in Example 289, a yellow compound (234 mg, yield; 32%) was obtained from 4-[4-(2-hydroxyethyl)piperazin-1-yl]-6-(4-hydroxyphenyl)thieno[3,2-c]pyridine (600 mg), ethyl bromoacetate (0.18 ml) and 3.0M methylmagnesium bromide/THF solution (1.7 ml). The resulting compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 139-142°C

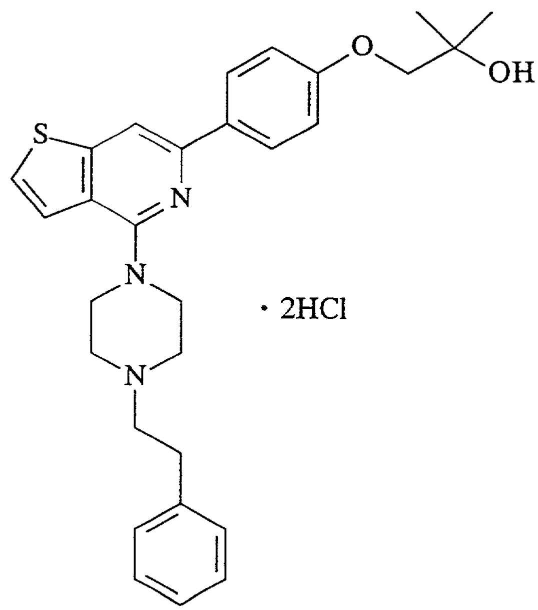
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.23(s,6H), 3.25-3.40(m,2H), 3.55(t,J=13.2Hz,44H), 3.65(d,J=12.0Hz,2H), 3.78(s,2H), 3.84(br,2H), 4.20(d,J=13.2Hz,2H), 7.05(d,J=8.8Hz,2H), 7.63(d,J=5.6Hz,1H), 7.79(d,J=5.6Hz,1H), 8.10(d,J=8.8Hz,2H), 8.19(s,1H).

MS(FAB) m/z 428(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.38(s,6H), 2.67(t,J=5.2Hz,2H), 2.78(t,J=5.2Hz,4H), 3.67-3.71(m,6H), 3.86(s,2H), 7.02(d,J=8.8Hz,2H), 7.38(d,J=5.6Hz,1H), 7.38(d,J=5.6Hz,1H), 7.74(s,1H), 8.04(d,J=8.8Hz,2H).

Example 297 Synthesis of 6-[4-(2-methyl-2-hydroxypropoxy)phenyl]-4-[4-(2-phenylethyl)piperazin-1-yl]thieno[3,2-c]pyridine



In the same manner as in Example 289, a yellow compound was obtained (485 mg, yield; 69%) from 4-(4-phenylethylpiperazin-1-yl)-6-(4-hydroxyphenyl)thieno[3,2-c]pyridine (605 mg), ethyl bromoacetate (0.18 ml) and 3.0M methylmagnesium bromide solution (1.2 ml). The resulting compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 140-142°C

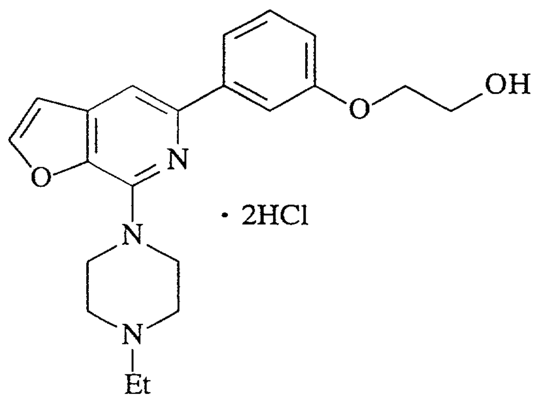
^{1}H-NMR(400MHz,DMSO-d_3); δ (ppm) 1.23(s,6H), 3.12-3.16(m,2H), 3.30-3.45(m,4H), 3.56(br-t,2H), 3.71(d,J=11.6Hz,2H), 3.78(s,2H), 4.23(d,J=14.0Hz,2H), 7.05(d,J=8.8Hz,2H), 7.23-7.39(m,5H), 7.63(d,J=5.6Hz,1H), 7.79(d,J=5.6Hz,1H), 8.01(d,J=8.8Hz,2H), 8.18(s,1H).

MS(FAB) m/z 488(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.38(s,6H), 2.69-2.74(m,2H), 2.78(t,J=4.8Hz,4H), 2.87-2.91(m,2H), 3.71(t,J=4.8Hz,4H), 3.86(s,2H), 7.44(d,J=8.8Hz,2H), 7.20-7.33(m,5H), 7.33(d,J=5.6Hz,1H), 7.40(d,J=5.6Hz,1H), 7.74(s,1H), 8.05(d,J=8.8Hz,2H).

Example 298 Synthesis of 7-(1-ethylpiperazin-4-yl)-5-[3-(2-hydroxyethoxy)phenyl]furo[2,3-c]pyridine dihydrochloride



In the same manner as in Example 301-4, the hydrochloride of the title compound was obtained as pale yellow crystals (215 mg, yield; 83%) from 7-(1-ethylpiperazin-4-yl)-5-bromofuro[2,3-c]pyridine (200 mg) and 3-tributylstannylphenoxyethyl acetate (563 mg).

Hydrochloride:

m.p.; 117-121°C

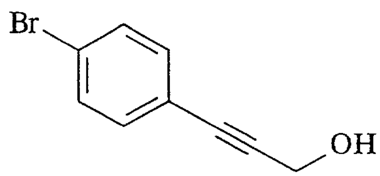
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.28(3H,t,J=7.2Hz), 3.07-3.18(2H,m), 3.56(2H,t,J=14.8Hz), 3.61(2H,d,J=11.6Hz), 3.74(2H,t,J=5Hz), 4.72(2H,d,J=14.8hz), 6.93(1H,dd,J=8Hz,2.4Hz), 7.02(1H,d,J=2.4Hz),

7.34(1H,t,J=8Hz), 7.60(1H,s), 7.61(1H,d,J=8Hz), 7.71(1H,s), 8.15(1H,d,J=2.4Hz), 11.00-11.10(1H,br-s).

FAB-Mass; 368(MH^+).

Example 299 Synthesis of 7-(1-ethylpiperazin-4-yl)-5-[4-(3-hydroxypropyl)phenyl]furo[2,3-c]pyridine dihydrochloride

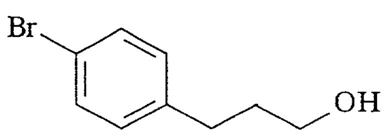
(299-1) 3-(4-Bromophenyl)-2-propyn-1-ol



In the same manner as in Example 139-1, the title compound was obtained as a yellow solid (13.792 g, yield; 93%) from 4-bromoiodobenzene (19.804 g) and propargyl alcohol (4.5 ml).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.75(1H,t,J=6.4Hz), 4.49(2H,d,J=6.4Hz), 7.30(2H,d,J=8.8Hz), 7.45(2H,d,J=8.8Hz).

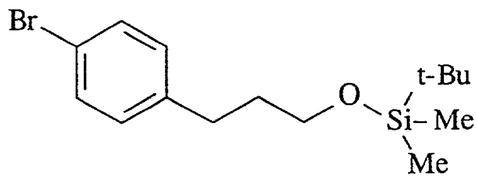
(299-2) 3-(4-Bromophenyl)-1-propanol



In the same manner as in Example 139-2, the title compound was obtained as a brown solid (4.64 g, yield; 88%) from 3-(4-bromophenyl)-2-propyn-1-ol (5.276 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.40(1H,br-s), 1.82-1.90(2H,m), 2.67(2H,t,J=7.8Hz), 3.66(2H,t,J=6.2Hz), 7.07(2H,d,J=8.8Hz), 7.40(2H,d,J=8.8Hz).

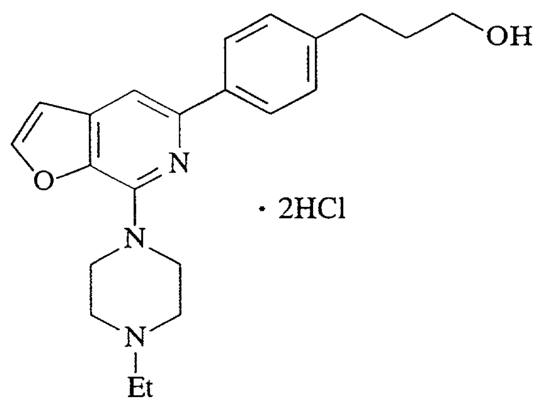
(299-3) 4-[3-(t-Butyldimethylsilyloxy)propyl]-1-bromobenzene



In the same manner as in Example 163-1, the title compound was obtained as a colorless oil (2.263 g, yield; 100%) from 3-(4-bromophenyl)-1-propanol (1.513 g) and t-butyldimethylsilyl chloride (1.161 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.04(6H,s), 0.90(9H,s), 1.76-1.83(2H,m), 2.63(2H,t,J=7.8Hz), 3.61(2H,t,J=6.2Hz), 7.06(2H,d,J=8.8Hz), 7.39(2H,d,J=8.8Hz).

(299-4) 7-(1-Ethylpiperazin-4-yl)-5-[4-(3-hydroxypropyl)phenyl]furo[2,3-c]pyridine



In the same manner as in Example 167-2, the hydrochloride of the title compound as colorless crystals (recrystallized from ethanol/isopropyl ether) (417 mg, yield; 83%) from 4-[3-(t-butyldimethylsilyloxy)propyl]-1-bromobenzene (2.263 g) and 7-(1-ethylpiperazin-4-yl)-5-bromofuro[2,3-c]pyridine (380 mg).

Hydrochloride:

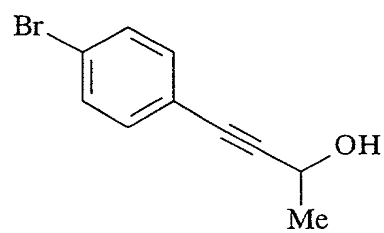
m.p.; 126-130°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.28(3H,t,J=7.2Hz), 1.63-1.78(2H,m), 2.63(2H,t,J=7.8Hz), 3.06-3.18(4H,m), 3.42(2H,t,J=6.4Hz), 3.56(2H,t,J=14.4Hz), 3.60(2H,d,J=10.8Hz), 4.73(2H,d,J=14.4Hz), 7.02(1H,d,J=2.4Hz), 7.26(2H,d,J=8.8Hz), 7.65(1H,s), 7.95(2H,d,J=8.8Hz), 8.13(1H,d,J=2.4Hz), 11.05(1H,br-s).

FAB-Mass; 366(MH$^+$).

Example 300 Synthesis of 7-(1-ethylpiperazin-4-yl)-5-[4-(3-hydroxybutyl)phenyl]furo[2,3-c]pyridine dihydrochloride

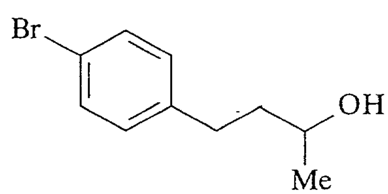
(300-1) 4-(4-Bromophenyl)-3-butyn-2-ol



In the same manner as in Example 139-1, the title compound was obtained as a brown solid (13.792 g, yield; 93%) from 4-bromoiodobenzene (16.609 g) and 3-butyn-2-ol (4.526 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.55(3H,d,J=6.8Hz), 1.85(1H,d,J=5.2Hz), 4.71-4.78(1H,m), 7.34(2H,d,J=8.8Hz), 7.44(2H,d,J=8.8Hz).

(300-2) 3-(4-Bromophenyl)-1-methyl-1-propanol

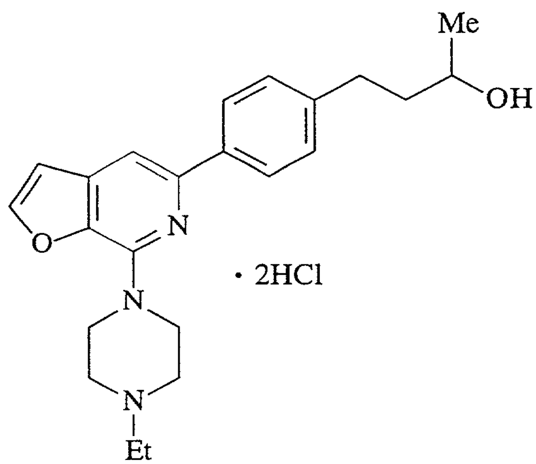


In the same manner as in Example 139-2, the title compound

was obtained as a brown oil (4.259 g, yield; 37%) from 4-(4-bromophenyl)-3-butyn-2-ol (11.791 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.23(3H,d,J=6Hz), 1.32(1H,s), 1.70-1.79(2H,m), 2.59-2.76(2H,m), 3.76-3.86(1H,m), 7.08(2H,d,J=8.8Hz), 7.40(2H,d,J=8.8Hz).

(300-3) 7-(1-Ethylpiperazin-4-yl)-5-[4-(3-hydroxybutyl)phenyl]furo[2,3-c]pyridine



3-(4-Bromophenyl)-1-methyl-1-propanol (2.186 g) and t-butyldimethylsilyl chloride (1.575 g) were treated in the same manner as in Example 163-1, to give 4-[3-(t-butyldimethylsilyloxy)-3-methylpropan-1-yl]-1-bromobenzene as a colorless oil (2.396 g). Subsequently, the resulting compound was treated with 7-(1-ethylpiperazin-4-yl)-5-bromofuro[2,3-c]pyridine (404 mg), in the same manner as in Example 167-2, to give the hydrochloride of the title compound as colorless crystals (recrystallized from ethanol/isopropyl ether) (390 mg, yield; 69%).

Hydrochloride:

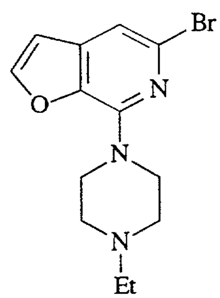
m.p.; 175-177°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.08(3H,d,J=6Hz), 1.28(3H,t,J=7.2Hz), 1.58-1.65(2H,m), 2.55-2.73(2H,m), 3.07-3.18(4H,m), 3.50-3.64(5H,m), 4.73(2H,d,J=14.8Hz), 7.01(1H,d,J=2.4Hz), 7.26(2H,d,J=8.8Hz), 7.65(1H,s), 7.94(2H,d,J=8.8Hz), 8.14(1H,d,J=2.4Hz), 10.95(1H,br-s).

FAB-Mass; 380(MH$^+$).

Example 301 Syntheiss of 7-(1-Ethylpiperazin-4-yl)-5-[4-(2-hydroxyethoxy)phenyl]furo[2,3-c]pyridine oxalate

(301-1) 7-(1-Ethylpiperazin-4-yl)-5-bromofuro[2,3-c]pyridine

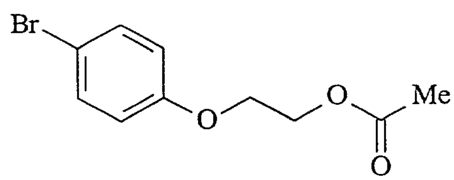


Phosphorus oxychloride (20.214 g) and phosphorus tribromide (40 ml) were added to 3-cyanomethyl-2-furancarboxylic acid (9.046 g) synthesized according to *Bull. Soc. chim. Fr.*, No. 5-6, II-270, 1978, and the resulting mixture was stirred at 140°C for 3 hr. After cooling as it was, ethanol was added thereto in small portions until exothermic reaction was ceased. The reaction solution was evaporated, and to the resulting residue was added 1-ethylpiperazine (240 ml), and the resulting mixture was stirred for 20 min, and then evaporated. The resulting residue was partitioned between ethyl acetate and

water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by (NH) silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a pale yellow solid (9.594 g, yield; 56%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.14(3H,t,J=7.2Hz), 2.47(2H,q,7J=.2Hz), 2.58(4H,t,J=5.2Hz), 3.92(4H,t,J=5.2Hz), 6.64(1H,d,J=2Hz), 7.02(1H,s), 7.60(1H,d,J=2Hz).

(301-2) 4-Bromophenoxyethyl acetate or compound identified by the following analysis data and synthetic procedures

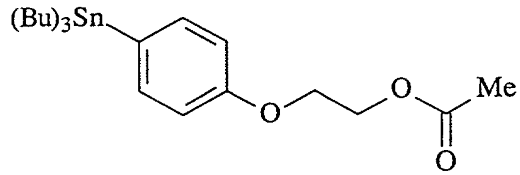


2-Bromophenol (26.128 g) was dissolved in N,N-dimethylformamide (70 ml), followed by the addition of 2-bromoethyl acetate (32.224 g) and potassium carbonate (21 g), and the mixture was stirred at 100°C overnight. After cooling as it was, the resulting insoluble matters were filtered off. The resulting filtrate was evaporated, and the resulting residue was purified by (NH) silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a pale yellow oil (33.915 g, yield; 87%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 2.10(3H,s), 4.14(2H,t,J=4.6Hz), 6.80(2H,d,J=8.8Hz), 7.38(2H,d,J=8.8Hz).

(301-3) 4-Tributylstannylphenoxyethyl acetate or compound identified by the following analysis data and synthetic

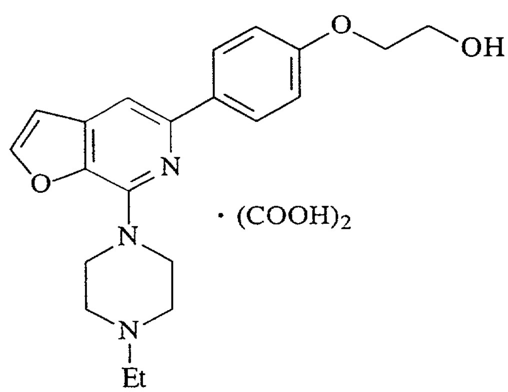
procedures



In the same manner as in Example 161-2, the title compound was obtained as a colorless oil (3.452 g, yield; 35%) from 4-bromophenoxyethyl acetate (5.182 g) and bis(tributyltin) (11 ml).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.88(9H,t,J=7.2Hz), 1.00-1.05(6H,m), 1.27-1.37(6H,m), 1.48-1.57(6H,m), 2.10(3H,s), 4.17(2H,t,J=4.8Hz), 6.91(2H,d,J=8.8Hz), 7.37(2H,d,J=8.8Hz).

(301-4) 7-(1-Ethylpiperazin-4-yl)-5-[4-(2-hydroxyethoxy)phenyl]furo[2,3-c]pyridine·oxalate



7-(1-Ethylpiperazin-4-yl)-5-bromofuro[2,3-c]pyridine (564 mg) and 4-tributylstannylphenoxyethyl acetate (3.452 g) were treated in the same manner as in Example 161-3, and the resulting product was dissolved in ethanol (16 ml), followed by the addition of a 1N aqueous solution of sodium hydroxide (6 ml), and the mixture was stirred at 70°C for 1 hr. The

reaction mixture was evaporated, and then partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by (NH) silica gel column chromatography (ethyl acetate/hexane system). Then, the resulting product was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as colorless crystals (417mg, yield; 90%).

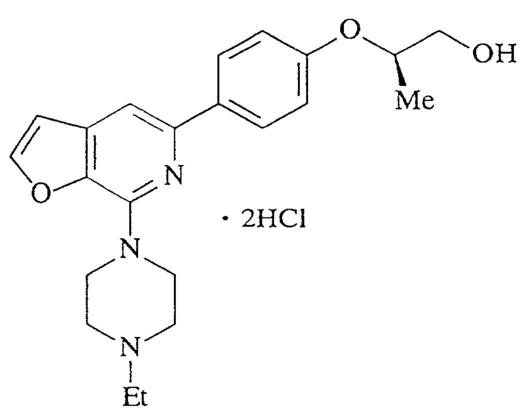
Oxalate:

m.p.; 145-152°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.19(3H,t,J=7.2Hz), 2.98(2H,q,J=7.2Hz), 3.14-3.22(4H,m), 3.72(2H,t,J=5Hz), 3.96-4.10(4H,br-s), 4.02(2H,t,J=5Hz), 6.98(1H,d,J=2Hz), 6.99(2H,d,J=8.8Hz), 7.57(1H,s), 7.98(2H,d,J=8.8Hz), 8.10(1H,d,J=2Hz).

FAB-Mass; 368(MH^+).

Example 302 Synthesis of 7-(1-ethylpiperazin-4-yl)-5-{4-[(R)-2-hydroxy-1-methylethoxy]phenyl}furo[2,3-c]pyridine dihydrochloride



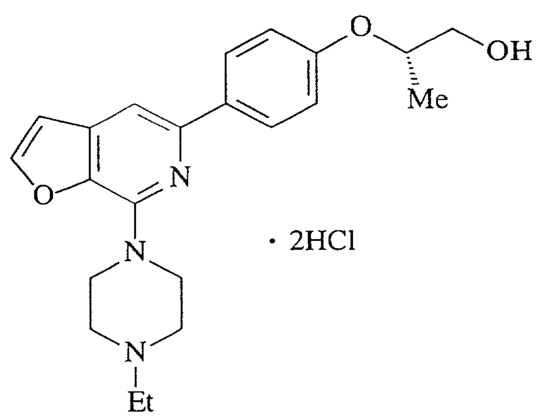
In the same manner as in Example 301-4, the hydrochloride of the title compound was obtained as a pale yellow amorphous (348 mg, yield; 67%) from 7-(1-ethylpiperazin-4-yl)-5-bromofuro[2,3-c]pyridine (373 mg) and 2-(4-tributylstannylphenoxy)-(R)-2-methylethyl acetate (889 mg).

Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.21(3H,d,J=6.4Hz), 1.28(3H,t,J=7.2Hz), 3.06-3.18(4H,m), 3.46(1H,dd,J=11.2Hz,5Hz), 3.56(2H,dd,J=11.2Hz,5.6Hz), 3.56-3.62(3H,m), 4.88-4.90(1H,m), 4.71(2H,d,J=14.4Hz), 6.99(2H,d,J=8.8Hz), 7.00(1H,d,J=2Hz), 7.59(1H,s), 7.96(2H,d,J=8.8Hz), 8.12(1H,d,J=2Hz), 11.15(1H,br-s).

FAB-Mass; 382(MH$^+$).

<u>Example 303 Synthesis of 7-(1-ethylpiperazin-4-yl)-5-{4-[(S)-2-hydroxy-1-methylethoxy]phenyl}furo[2,3-c]pyridine dihydrochloride</u>



In the same manner as in Example 301-4, the hydrochloride of the title compound was obtained as a pale yellow amorphous (348 mg, yield; 67%) from 7-(1-ethylpiperazin-4-yl)-5-

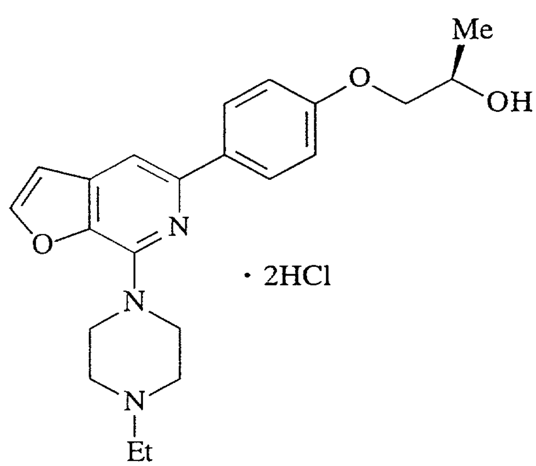
bromofuro[2,3-c]pyridine (373 mg) and 2-(4-tributylstannylphenoxy)-(S)-2-methylethyl acetate (889 mg).

Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.21(3H,d,J=6Hz), 1.28(3H,t,J=7.2Hz), 3.05-3.18(4H,m), 3.46(1H,dd,J=11.2Hz,4.8Hz), 3.54(1H,dd,J=11.2Hz,5.6Hz), 3.60(4H,t,J=11.2Hz), 4.43-4.50(1H,m), 4.71(2H,d,J=14.4Hz), 6.99(2H,d,J=8.8Hz), 7.00(1H,d,J=2.4Hz), 7.50(1H,s), 7.96(2H,d,J=8.8Hz), 8.13(1H,d,J=2.4Hz), 11.20(1H,br-s).

FAB-Mass; 382(MH^+).

Example 304 Synthesis of 7-(1-ethylpiperazin-4-yl)-5-{4-[(S)-2-hydroxypropoxy]phenyl}furo[2,3-c]pyridine dihydrochloride



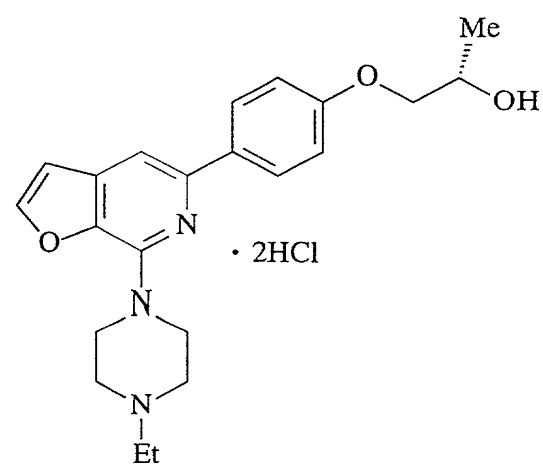
In the same manner as in Example 301-4, the hydrochloride of the title compound was obtained as a pale yellow amorphous (348 mg, yield; 67%) from 7-(1-ethylpiperazin-4-yl)-5-bromofuro[2,3-c]pyridine (373 mg) and 2-(4-tributylstannylphenoxy)-(S)-1-methylethyl acetate (889 mg).

Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.15(3H,d,J=6.4Hz), 1.28(3H,t,J=7.2Hz), 3.05-3.18(4H,m), 3.57(2H,t,J=14.4Hz), 3.59(2H,d,J=12.4Hz), 3.79-3.88(2H,m), 3.92-4.00(1H,m), 4.71(2H,d,J=14.4Hz), 6.98(2H,d,J=8.8Hz), 6.99(1H,d,J=2Hz), 7.60(1H,d,J=2Hz), 7.60(1H,s), 7.99(2H,d,J=8.8Hz), 8.12(1H,d,J=2Hz), 11.65(1H,br-s).

FAB-Mass; 382(MH^+).

Example 305 Synthesis of 7-(1-ethylpiperazin-4-yl)-5-{4-[(R)-2-hydroxypropoxy]phenyl}furo[2,3-c]pyridine dihydrochloride



In the same manner as in Example 301-4, the hydrochloride of the title compound was obtained as a pale yellow amorphous (73 mg, yield; 17%) from 7-(1-ethylpiperazin-4-yl)-5-bromofuro[2,3-c]pyridine (373 mg) and 2-(4-tributylstannylphenoxy)-(R)-1-methylethyl acetate (920 mg).

Hydrochloride:

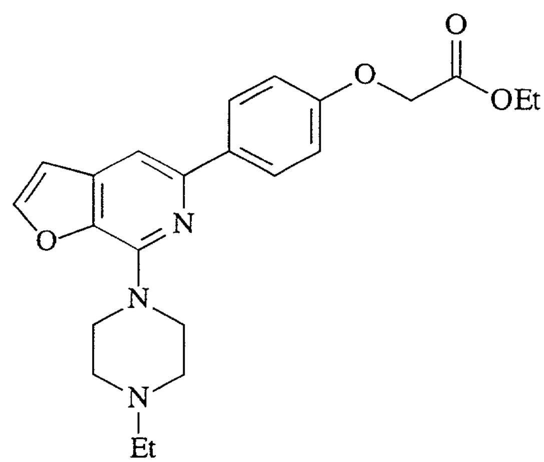
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.15(3H,d,J=6.4Hz),

1.28(3H,t,J=7.2Hz), 3.06-3.18(4H,m), 3.52-3.62(4H,m), 3.79-3.88(2H,m), 3.91-3.99(1H,m), 4.72(2H,d,J=14.8Hz), 6.98(2H,d,J=8.8Hz), 6.99(1H,d,J=2Hz), 7.60(1H,s), 7.97(2H,d,J=8.8Hz), 8.12(1H,d,J=2Hz), 11.10(1H,br-s).

FAB-Mass; 382(MH^+).

Example 306 Synthesis of 7-(1-ethylpiperazin-4-yl)-5-[4-(3-hydroxy-3-methylbutoxy)phenyl]furo[2,3-c]pyridine dihydrochloride

(306-1) 7-(1-Ethylpiperazin-4-yl)-5-[(4-ethoxycarbonylmethoxy)phenyl]furo[2,3-c]pyridine

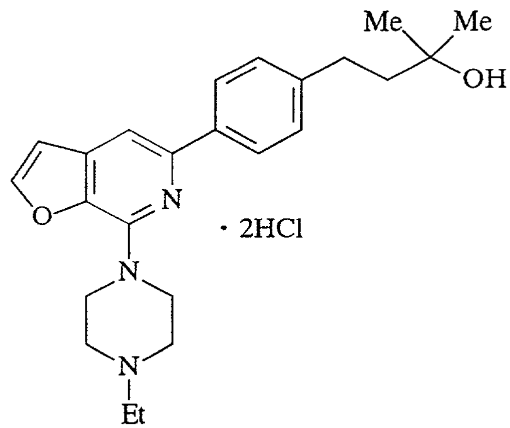


In the same manner as in Example 161-3, the titled compound was obtained as a colorless oil (484 mg, yield; 80%) from 7-(1-ethylpiperazin-4-yl)-5-bromofuro[2,3-c]pyridine (465 mg) and ethyl 2-(4-tributylstannylphenoxy)acetate.

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(3H,t,J=7.2Hz), 1.31(3H,t,J=7.2Hz), 2.50(2H,q,J=7.2Hz), 2.65(4H,t,J=5Hz), 3.99(4H,t,J=5Hz), 4.29(2H,q,J=7.2Hz), 4.67(1H,s), 6.73(1H,d,J=2.4Hz), 6.97(2H,d,J=8.8Hz), 7.32(1H,s),

7.61(1H,d,J=2.4Hz), 7.98(2H,d,J=8.8Hz).

(306-2) 7-(1-Ethylpiperazin-4-yl)-5-[4-(3-hydroxy-3-methylbutoxy)phenyl]furo[2,3-c]pyridine dihydrochloride



In the same manner as in Example 260-3, the hydrochloride of the titled compound was obtained as a colorless solid (435 mg, yield; 75%) from 7-(1-ethylpiperazin-4-yl)-5-[(4-ethoxycarbonylmethoxy)phenyl]furo[2,3-c]pyridine (484 mg) and 3M methylmagnesium bromide/ether solution (2 ml).

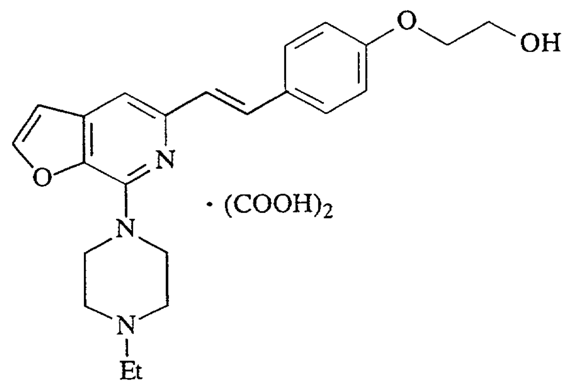
Hydrochloride:

m.p.; 123-125°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.20(6H,s), 1.28(3H,t,J=7.2Hz), 3.10-3.18(4H,m), 3.56(2H,t,J=14.4Hz), 3.60(2H,d,J=11.2Hz), 4.71(2H,d,J=14.4Hz), 6.99(2H,d,J=8.8Hz), 7.00(1H,d,J=2Hz), 7.60(1H,s), 7.98(2H,d,J=8.8Hz), 8.12(1H,d,J=2Hz), 11.05-11.15(1H,br-s).

FAB-Mass; 396(MH^+).

Example 307 Synthesis of 7-(1-ethylpiperazin-4-yl)-5-{trans-2-[4-(2-hydroxyethoxy)phenyl]ethenyl}furo[2,3-c]pyridine oxalate



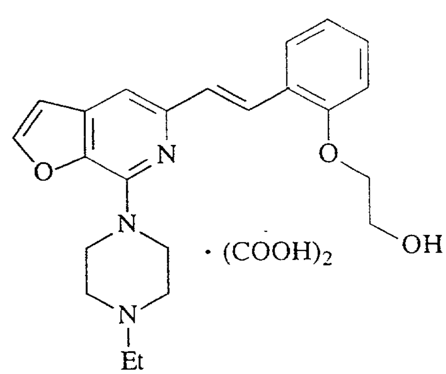
In the same manner as in Example 189, the oxalate of the title compound was obtained as a yellow amorphous (106 mg, yield; 17%) from 7-(1-ethylpiperazin-4-yl)-5-bromofuro[2,3-c]pyridine (372 mg) and 2-(4-vinylphenoxy)ethanol (264 mg).

Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.21(3H,t,J=7.2Hz), 3.03(2H,q,J=7.2Hz), 3.16-3.26(4H,m), 3.71(2H,t,J=5Hz), 3.94-4.14(4H,m), 3.99(2H,t,J=5Hz), 6.94(2H,d,J=8.8Hz), 6.97(1H,d,J=2Hz), 7.08(1H,d,J=16Hz), 7.15(1H,s), 7.46(1H,d,J=16Hz), 7.53(2H,d,J=8.8Hz), 8.08(1H,d,J=2Hz).

FAB-Mass; 394(MH$^+$).

Example 308 Synthesis of 7-(1-ethylpiperazin-4-yl)-5-{trans-2-[2-(2-hydroxyethoxy)phenyl]ethenyl}furo[2,3-c]pyridine oxalate



In the same manner as in Example 189, the oxalate of the title compound was obtained as a yellow amorphous (366 mg, yield; 67%) from 7-(1-ethylpiperazin-4-yl)-5-bromofuro[2,3-c]pyridine (372 mg) and 2-(2-vinylphenoxy)ethanol (246 mg).

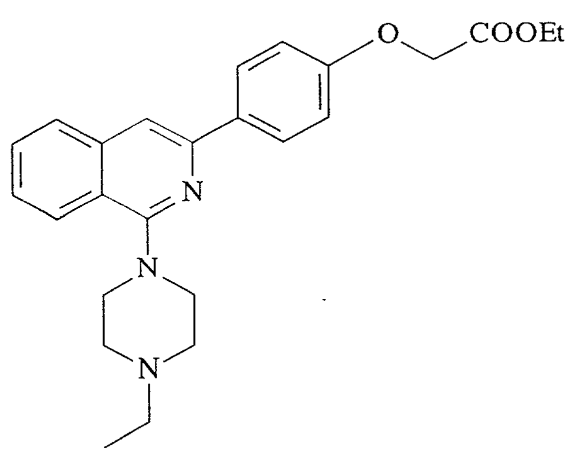
Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.21(3H,t,J=7.2Hz), 3.02(2H,q,J=7.2Hz), 3.14-3.26(4H,m), 3.80(2H,t,J=5Hz), 4.05(2H,t,J=5Hz), 6.96(1H,dd,J=7.8Hz,7.4Hz), 6.98(1H,d,J=2.4Hz), 7.03(1H,d,J=8.2Hz), 7.16(1H,s), 7.23(1H,dd,J=8.2Hz,7.4Hz), 7.24(1H,d,J=15.6Hz), 7.65(1H,dd,J=7.8Hz,2Hz), 7.88(1H,d,J=15.6Hz), 8.09(1H,d,J=2.4Hz).

FAB-Mass; 394(MH$^+$).

Example 309 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[4-(2-hydroxy-2-methylpropoxy)phenyl]isoquinoline dihydrochloride

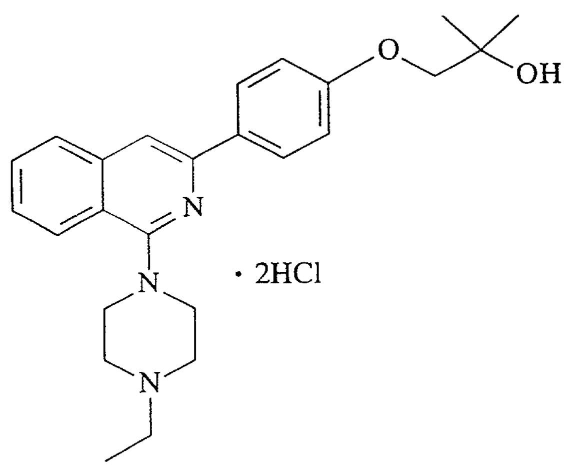
(309-1) 1-(1-Ethylpiperazin-4-yl)-3-[(4-ethoxycarbonylmethoxy)phenyl]isoquinoline or compound identified by the following analysis data and synthetic procedures



In the same manner as in Example 161-3, the title compound was obtained as a pale yellow oil (473 mg, 73%) from 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (480 mg) and ethyl 2-(4-tributylstannylphenoxy)acetate.

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(3H,t,J=7.2Hz), 1.32(3H,t,J=7.2Hz), 2.55(2H,q,J=7.2Hz), 2.75(4H,t,J=4.4Hz), 3.58(4H,t,J=4.4Hz), 4.29(2H,q,J=7.2Hz), 4.68(2H,s), 7.01(2H,d,J=8.8Hz), 7.43(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.56(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.61(1H,s), 7.76(1H,d,J=8Hz), 8.06(1H,d,J=8Hz), 8.12(2H,d,J=8.8Hz).

(309-2) 1-(1-Ethylpiperazin-4-yl)-3-[4-(2-hydroxy-2-methylpropoxy)phenyl]isoquinoline dihydrochloride or compound identified by the following analysis data and synthetic procedures



In the same manner as in Example 260-3, the hydrochloride of the title compound was obtained as yellow crystals (172 mg, yield; 36%) from 1-(1-ethylpiperazin-4-yl)-3-[(4-ethoxycarbonylmethoxy)phenyl]isoquinoline (473 mg) and 3M

methylmagnesium bromide/ether solution (1.8 ml).

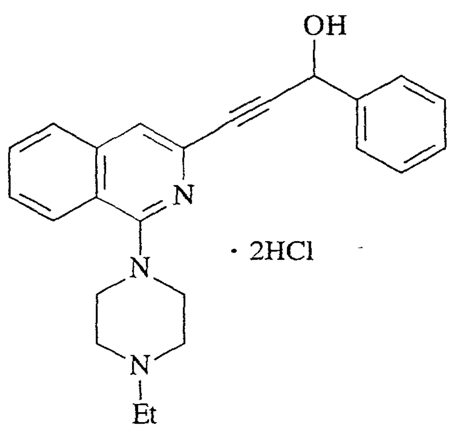
Hydrochloride:

m.p.; 129-134°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.21(6H,s), 1.31(3H,t,J=7.2Hz), 3.20(1H,q,J=7.2Hz), 3.22(1H,q,J=7.2Hz), 3.31(1H,t,J=11.2Hz), 3.34(1H,t,J=11.2Hz), 3.60(2H,d,J=1.2Hz), 3.77(2H,s), 3.95(2H,d,J=13.6Hz), 7.05(2H,d,J=8.8Hz), 7.55(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.70(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.93(1H,dd,J=8Hz,1.2Hz), 7.98(1H,s), 8.07(1H,dd,J=8Hz,1.2Hz), 8.13(2H,d,J=8.8Hz), 11.15(1H,br-s).

FAB-Mass; 406(MH$^+$).

Example 310 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(3-phenyl-3-hydroxy-1-propynyl)isoquinoline hydrochloride



In the same manner as in Example 177, the title compound was obtained as a brown solid (1.222 g, yield; 77%) from 1-phenyl-2-propyn-1-ol (858 mg) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (1.386 mg).

The resulting compound was converted into a hydrochloride in a conventional manner.

Hydrochloride:

m.p.; 203-209°C

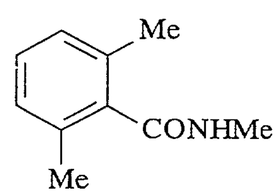
Free form:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.15(3H,t,J=7.2Hz), 2.54(2H,q,7J=.2Hz), 2.72(4H,t,J=4.4Hz), 3.51(4H,t,J=4.4Hz), 5.76(1H,s), 7.32-7.53(5H,m), 7.59(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.65-7.70(3H,m), 8.04(1H,dd,J=8Hz,1.2Hz).

ESI-Mass; 372(MH^+).

Example 311 Synthesis of 1-(1-ethylpiperazin-4-yl)-8-methyl-3-(4-methoxyphenyl)isoquinoline hydrochloride

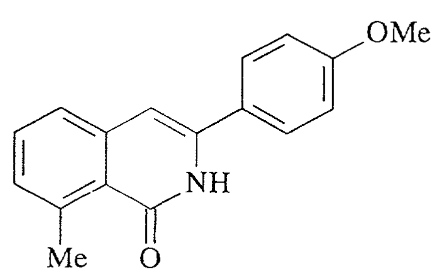
(311-1) 2,6-Dimethyl-N-methylbenzamide or compound identified by the following analysis data and synthetic procedures



In the same manner as in Example 225-1, the title compound was obtained as a colorless solid (10.761 g, yield; 100%) from 2,6-dimethylbenzoic acid (10.125 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 2.31(6H,s), 3.02(3H,d,J=4.8Hz), 5.64(1H,br-s), 7.01(2H,d,J=8Hz), 7.15(1H,t,J=8Hz).

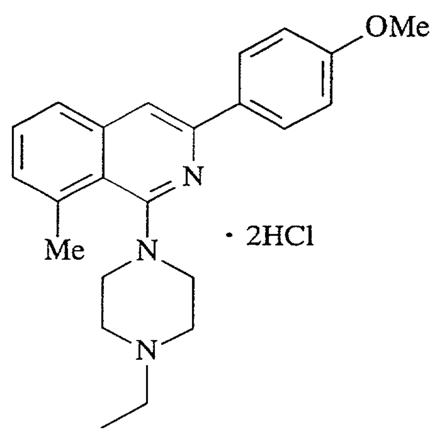
(311-2) 8-Methyl-3-(4-methoxyphenyl)isoquinolin-1-(2H)-one



In the same manner as in Example 10, the title compound was obtained as a colorless solid (168 mg, yield; 2%) from 2,6-dimethyl-N-methylbenzamide (4.986 g) and anisonitrile (4.128 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 2.96(3H,s), 3.88(3H,s), 6.65(1H,s), 7.01(2H,d,J=8.8Hz), 7.18(1H,d,J=7.6Hz), 7.38(1H,d,J=7.6Hz), 7.47(1H,t,J=7.6Hz), 7.74(2H,d,J=8.8Hz), 10.41(1H,br-s).

(311-3) 1-(1-Ethylpiperazin-4-yl)-8-methyl-(4-methoxyphenyl]isoquinoline hydrochloride



5-Methyl-3-(4-methoxyphenyl)isoquinolin-1-(2H)-one (168 mg) was treated in the same manner as in Example 252-3, to give the hydrochloride of the title compound (recrystallized from ethanol/isopropyl ether) (215 mg, yield; 78%) as yellow crystals.

Hydrochloride:

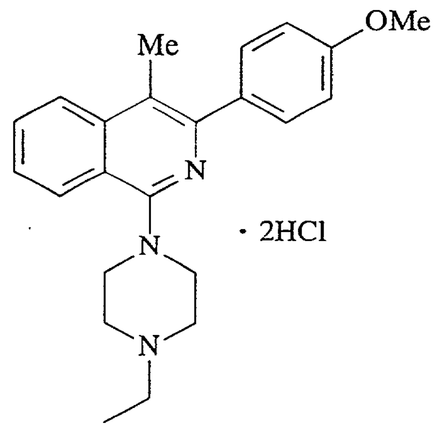
m.p.; 248-253°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.31(3H,t,J=7.2Hz), 2.68(3H,s), 3.20(1H,q,J=7.2Hz), 3.22(1H,q,J=7.2Hz), 3.31(1H,t,J=10.5Hz),

3.34(1H,t,J=10.5Hz), 3.48(2H,t,J=13.6Hz), 3.60(2H,d,J=10.5Hz), 3.81(3H,s), 3.93(2H,d,J=13.6Hz), 7.05(2H,d,J=8.8Hz), 7.44(1H,dd,J=8.2Hz,6.8Hz), 7.54(1H,d,J=6.8Hz), 7.93(1H,d,J=8.2Hz), 7.93(1H,s), 8.18(2H,d,J=8.8Hz), 10.95(1H,br-s).

ESI-Mass; 362(MH^+).

Example 312 Synthesis of 1-(1-ethylpiperazin-4-yl)-4-methyl-3-(4-methoxyphenyl)isoquinoline hydrochloride



In the same manner as in Example 252-3, 1-(-ethylpiperazin-4-yl)-4-chloro-3-(4-methoxyphenyl)isoquinoline (318 mg), 3M methylmagnesium bromide/ether solution (5.3 ml) and [1,3-bis(diphenylphosphino)propane]nickel(II) chloride (70 mg) were dissolved and suspended in toluene (14 ml), and then the mixture was stirred in nitrogen atmosphere at 80°C for 4 days and treated, to give the hydrochloride of the title compound as a pale yellow amorphous (36 mg, yield; 10%).

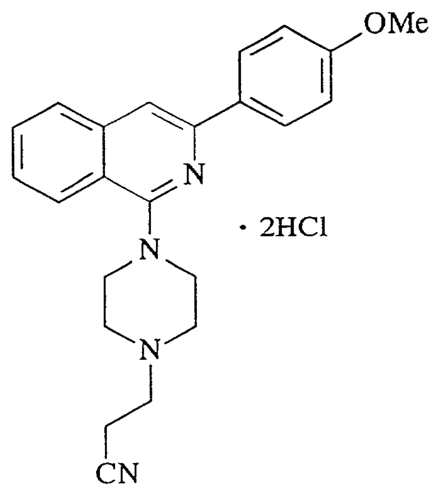
Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.30(3H,t,J=7.2Hz), 2.52(3H,s),

3.18(1H,q,J=7.2Hz), 3.19(1H,q,J=7.2Hz), 3.29(1H,t,J=10.7Hz), 3.32(1H,t,J=10.7Hz), 3.47-3.56(4H,m), 3.81(3H,s), 3.85(2H,d,J=13.6Hz), 7.04(2H,d,J=8.8Hz), 7.56(2H,d,J=8.8Hz), 7.65(1H,t,J=8.4Hz), 7.83(1H,t,J=8.4Hz), 8.08(1H,d,8.4Hz), 10.30(1H,br-s).

ESI-Mass; 362(MH^+).

Example 313 Synthesis of 1-[1-(2-cyanoethyl)piperazin-4-yl]-3-(4-methoxyphenyl)isoquinoline dihydrochloride or compound identified by the following analysis data and synthetic procedures



In the same manner as in Example 236-3, the hydrochloride of the title compound was obtained as yellow crystals (recrystallized from ethanol) (346 mg, yield; 80%) from 1-piperazinyl-3-(4-methoxyphenyl)isoquinoline (319 mg) and 3-bromopropionitrile (100 ml).

Hydrochloride:

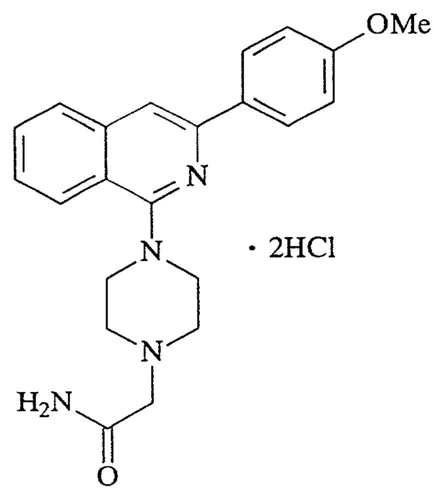
m.p.; 164-166°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 3.23(2H,t,J=7.2Hz), 3.38-

3.54(4H,m), 3.57(2H,t,J=7.2Hz), 3.60-3.68(2H,br-d), 3.81(3H,s), 3.96-4.04(2H,br-d), 7.05(2H,d,J=8.8Hz), 7.56(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.70(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.93(1H,d,J=8Hz), 7.98(1H,s), 8.07(1H,d,J=8Hz), 8.13(2H,d,J=8.8Hz).

ESI-Mass; 373(MH^+).

Example 314 Synthesis of 1-[1-(carbamoylmethyl)piperazin-4-yl]-3-(4-methoxyphenyl)isoquinoline dihydrochloride



In the same manner as in Example 236-3, the hydrochloride of the title compound was obtained as yellow crystals (recrystallized from ethanol/isopropyl ether) (228 mg, yield; 50%) from 1-piperazinyl-3-(4-methoxyphenyl)isoquinoline (319 mg) and bromoacetamide (166 mg).

Hydrochloride:

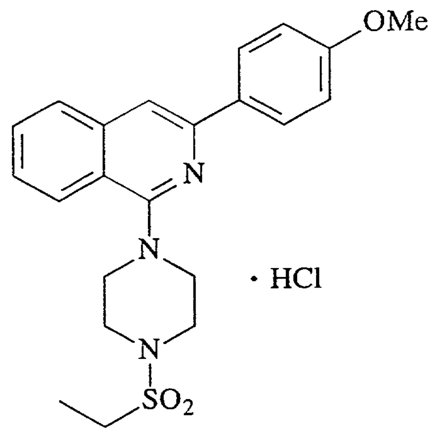
m.p.; 153-155°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 3.46-3.57(4H,m), 3.58-3.66(2H,m), 3.81(3H,s), 3.92-4.02(2H,br-d), 4.05(2H,s), 7.05(2H,d,J=8.8Hz), 7.55(1H,ddd,J=8Hz,7Hz,1.2Hz),

7.70(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.73(1H,s), 7.93(1H,d,J=8Hz), 7.97(1H,s), 8.06(1H,d,J=8Hz), 8.07(1H,s), 8.13(2H,d,J=8.8Hz).

ESI-Mass; 377(MH^+).

Example 315 Synthesis of 1-(4-ethylsulfonylpiperazin-1-yl)-3-(4-methoxyphenyl)isoquinoline hydrochloride



1-Piperazinyl-3-(4-methoxyphenyl)isoquinoline (140 mg) was dissolved in tetrahydrofuran (2 ml), followed by the addition of triethylamine (0.12 ml) and ethynylsulfonyl chloride (0.08 ml), and the mixture was reacted for 2 hr. The reaction solution was partitioned between ethyl acetate and a 2N aqueous solution of sodium hydroxide. The resulting organic layer was washed with water and brine and dried. The resulting product was recrystallized from hexane/ethyl acetate, to give the title compound (139 mg, yield; 77%). The resulting compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.28(t,J=7.2Hz,3H),

3.18(q,J=7.2Hz,2H), 3.52(br,8H), 3.83(s,3H),

7.07(d,J=8.8Hz,2H), 7.57(d,J=8.0Hz,1H), 7.72(d,J=8.0Hz,1H),

7.94(d,J=8.0Hz,1H), 7.95(s,1H), 8.10(d,J=8.0Hz,1H),

8.14(d,J=8.8Hz,2H).

MS(FAB) m/z 412$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.44(t,J=7.6Hz,3H),

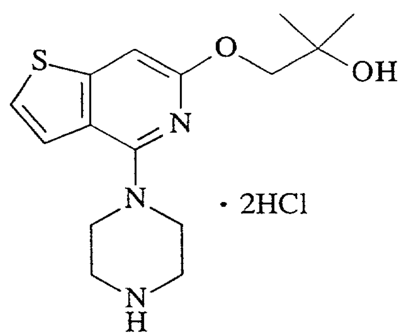
3.05(q,J=7.6Hz,2H), 3.61(br,8H), 3.88(s,3H),

7.01(d,J=8.8Hz,2H), 7.47(ddd,J=8.4,8.0,1.2Hz,1H),

7.60(ddd,J=8.4,8.0,1.2Hz,1H), 7.68(s,1H), 7.80(d,J=8.0Hz,1H),

8.01(d,J=8.4Hz,1H), 8.09(d,J=8.8Hz,2H).

Example 316 Synthesis of 4-piperidinyl-6-[4-(2-methyl-2-hydroxypropoxy)phenyl]thieno[3,2-c]pyridine hydrochloride



In the same manner as in Example 289, an oil was obtained from 4-[4-(t-butoxycarbonyl)piperazin-1-yl]-6-(4-hydroxyphenyl)thieno[3,2-c]pyridine (872 mg), ethyl bromoacetate (0.32 ml) and 3.0M ethylmagnesium bromide/THF solution (1.7 ml). THF (10 ml) and a 5N aqueous solution of hydrochloric acid (2 ml) were added to the resulting oil, and the mixture was heated under reflux at 60°C for 20 min. The

reaction solution was cooled, and then basified with an aqueous solution of saturated sodium bicarbonate. Then, the mixture was extracted with ethyl acetate. The resulting organic layer was washed with water, dried and concentrated. The resulting residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate system), to give the free compound of the title compound as a colorless oil (534 mg, yield; 66%). The resulting free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as white crystals.

Hydrochloride:

m.p.; 154-156°C

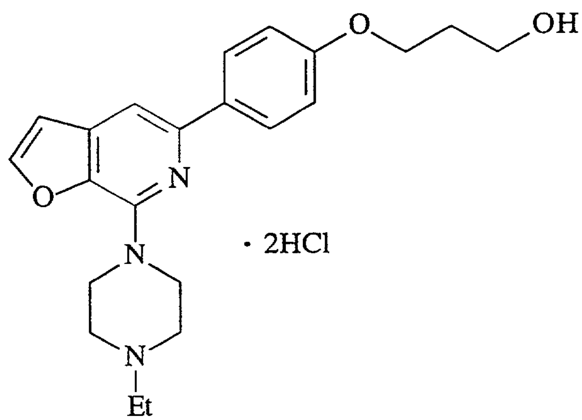
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.23(s,6H), 3.34(br,4H), 3.73(br,4H), 3.78(s,2H), 7.04(d,J=8.8Hz,2H), 7.62(d,J=5.2Hz,1H), 7.77(d,J=5.2Hz,1H), 8.09(d,J=8.8Hz,2H), 8.18(s,1H).

MS(FAB) m/z 384(M+H)$^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.37(s,6H), 3.12(t,J=4.8Hz,4H), 3.61(t,J=4.8Hz,4H), 3.86(s,2H), 7.00(d,J=8.8Hz,2H), 7.32(d,J=5.6Hz,1H), 7.39(d,J=5.6Hz,1H), 7.73(s,1H), 8.04(d,J=8.8Hz,2H).

Example 317 Synthesis of 7-(1-ethylpiperazin-4-yl)-5-[4-(3-hydroxypropoxy)phenyl]furo[2,3-c]pyridine dihydrochloride



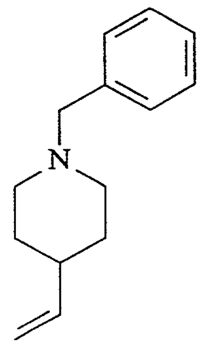
In the same manner as in Example 161-2, the hydrochloride of the title compound was obtained as a colorless amorphous (353 mg, yield; 67%) from 7-(1-ethylpiperazin-4-yl)-5-bromofuro[2,3-c]pyridine (373 mg) and 1-(4-tributylstannylphenoxy)-3-tetrahydropyranyloxypropane (1.404 g).

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.28(3H,t,J=7.2Hz), 1.86(2H,qui,J=6.4Hz), 3.06-3.18(4H,m), 3.50-3.62(6H,m), 4.07(2H,t,J=6.4Hz), 4.72(2H,d,J=14.4Hz), 6.99(2H,d,J=8.8Hz), 7.00(1H,d,J=2Hz), 7.60(1H,m), 7.97(2H,d,J=8.8Hz), 8.12(1H,d,J=2Hz).

FAB-Mass; 382(MH^+).

Example 318 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(4-methoxyphenyl)isoquinoline hydrochloride

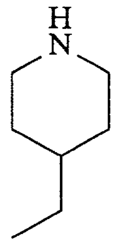
(318-1) 1-Benzyl-4-(1-ethynyl)piperidine



Ethyl triphenylphosphonium bromide (25 g) was suspended in tetrahydrofuran (100 ml), followed by the addition of 60% sodium hydride (2.68 g) under ice-cooling, and the mixture was stirred at room temperature for 2 hr. The reaction solution was ice-cooled again, followed by the addition of 1-benzyl-4-piperidone (11.55 g), and the resulting mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a colorless oil (6.08 g, yield; 52%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.57(3H,d,J=6.8Hz), 2.19(2H,t,J=5.6Hz), 2.26(2H,t,J=5.6Hz), 2.40(2H,t,J=5.6Hz), 2.41(2H,t,J=5.6Hz), 3.51(2H,s), 5.18(1H,q,J=6.8Hz), 7.22-7.36(5H,m).

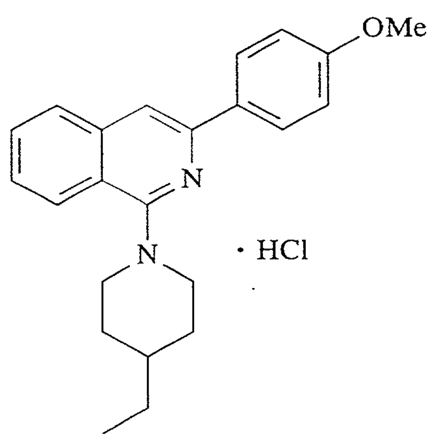
(318-2) 4-Ethylpiperidine



1-Benzyl-4-(1-ethylene)piperidine (6.084 g) was dissolved in methanol (60 ml), followed by the addition of 20% palladium hydroxide/carbon catalyst (617 mg), and the resulting mixture was stirred in hydrogen atmosphere overnight at room temperature. After the resulting insoluble matters were filtered off, the resulting filtrate was evaporated and partitioned between methylene chloride and an aqueous solution of saturated sodium bicarbonate; the resulting organic layer was dried (over $MgSO_4$) and evaporated, to give the title compound as a pale yellow oil (1.042 g, yield; 28%).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.89(3H,t,J=7.2Hz), 1.18-1.33(5H,m), 1.75(2H,d,J=12Hz), 2.66(2H,t,J=11.6Hz), 3.19(2H,d,J=11Hz), 5.00(1H,br-s).

(318-3) 1-(4-Ethylpiperidin-1-yl)-3-(4-methoxyphenyl)isoquinoline hydrochloride



1-Chloro-3-(4-methoxyphenyl)isoquinoline (405 mg) and 4-ethylpiperidine (168 mg) were dissolved in N,N-dimethylformamide (5 ml), followed by the addition of triethylamine (251 ml), and the mixture was stirred at 80°C overnight. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system). Then the resulting product was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/isopropyl ether, to give the hydrochloride of the title compound as a colorless crystals (87 mg, yield; 13%).

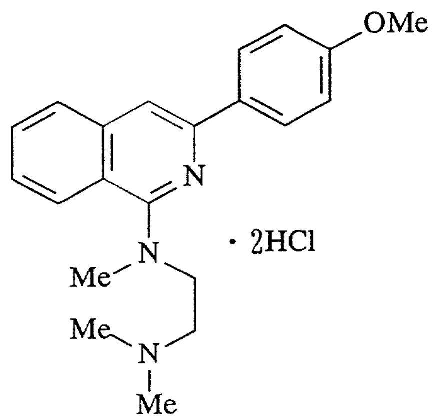
Hydrochloride:

m.p.; 109-114°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.92(3H,t,J=7.2Hz), 1.30-1.38(2H,br-quin), 1.40-1.53(3H,m), 1.80-1.90(2H,br-d), 3.02-3.12(2H,br-t), 3.88-3.98(2H,br-d), 7.05(2H,d,J=8.8Hz), 7.56(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.72(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.83(1H,s), 7.90(1H,d,J=8Hz), 8.03(1H,d,J=8Hz), 8.05(2H,d,J=8.8Hz).

ESI-Mass; 347(MH^+).

Example 319 Synthesis of 1-{N-[2-(2-dimethylamino)ethyl]-N-methylamino}-3-(4-methoxyphenyl)isoquinoline dihydrochloride



In the same manner as in Example 2, the hydrochloride of the title compound was obtained as yellow crystals (recrystallized in ethanol/isopropyl ether) (433 mg, yield; 58%) from 1-chloro-3-(4-methoxyphenyl)isoquinoline (514 mg) and N,N,N'-trimethylethylenediamine (4.8 ml).

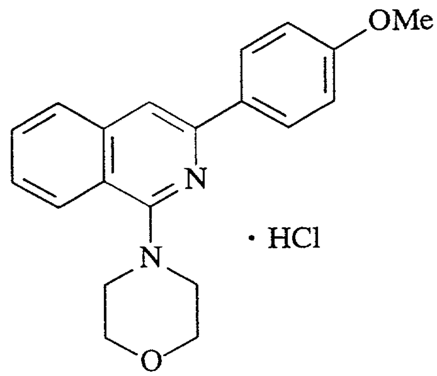
Hydrochloride:

m.p.; 160-162°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 2.79(3H,s), 2.81(3H,s), 3.13(3H,s), 3.45(1H,t,J=6.4Hz), 3.46(1H,t,J=6.4Hz), 3.81(3H,s), 3.87(2H,t,J=6.4Hz), 7.04(2H,d,J=8.8Hz), 7.52(1H,ddd,J=8Hz,6.8Hz,1.2Hz), 7.61(1H,ddd,J=8Hz,6.8Hz,1.2Hz), 7.87(1H,s), 7.89(1H,d,J=8Hz), 8.11(2H,d,J=8.8Hz), 8.18(1H,d,J=8Hz), 10.08(1H,br-s).

ESI-Mass; 336(MH^{+}).

Example 320 Synthesis of 1-(4-morpholinyl)-3-(4-methoxyphenyl)isoquinoline hydrochloride



In the same manner as in Example 2, the hydrochloride of the title compound was obtained as yellow crystals (recrystallized in ethanol) (371 mg, yield; 56%) from 1-chloro-3-(4-methoxyphenyl)isoquinoline (468 mg) and morpholine (3.1 ml).

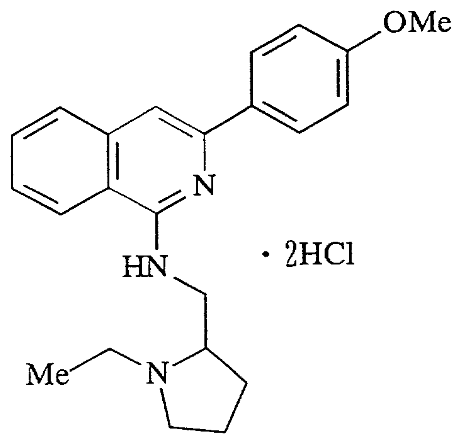
Hydrochloride:

m.p.; 137-139°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 3.38(4H,t,J=4.4Hz), 3.80(3H,s), 3.87(4H,t,J=4.4Hz), 7.04(2H,d,J=8.8Hz), 7.51(1H,ddd,J=8.4Hz,7Hz,1.2Hz), 7.66(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.89(1H,d,J=8Hz), 7.90(1H,s), 8.07(1H,d,J=8.4Hz), 8.13(2H,d,J=8.8Hz).

ESI-Mass; 321(MH^+).

Example 321 Synthesis of 1-(1-ethyl-2-pyrrolidinyl)methylamino-3-(4-methoxyphenyl)isoquinoline dihydrochloride



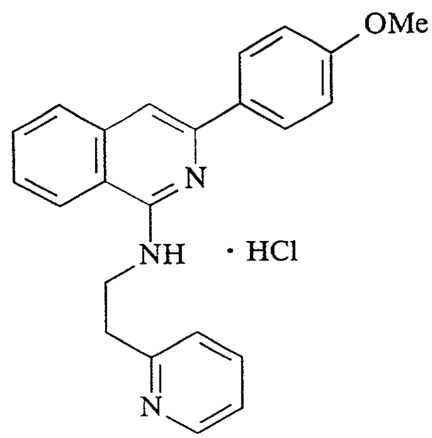
In the same manner as in Example 2, the hydrochloride of the title compound was obtained as a brown amorphous (85 mg, yield; 11%) from 1-chloro-3-(4-methoxyphenyl)isoquinoline (486 mg) and 2-aminomethyl-1-ethylpyrrolidine (5.2 ml).

Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.18(3H,t,J=6.8Hz), 1.20-1.35(1H,m), 1.85-2.00(4H,m), 2.15-2.25(1H,m), 3.03-3.15(2H,m), 3.35-3.45(1H,m), 3.50-3.60(1H,m), 3.85-3.95(1H,m), 3.95-4.05(1H,m), 4.15-4.25(1H,m), 7.05(2H,d,J=8.8Hz), 7.47(1H,s), 7.50-7.58(1H,m), 7.66-7.75(1H,m), 7.82(1H,d,J=8.4Hz), 7.98(2H,d,J=8.8Hz), 8.38-8.54(1H,m).

ESI-Mass; 362(MH^+).

Example 322 Synthesis of 3-(4-methoxyphenyl)-1-[2-(2-pyridyl)ethyl]aminoisoquinoline hydrochloride



In the same manner as in Example 10-1, the free compound of the title compound was obtained (107 mg, yield; 69%) from 1-chloro-3-(4-methoxyphenyl)isoquinoline (117 mg) and 2-(2-aminoethyl)pyridine (0.52 ml). The resulting free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 138-140°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 3.30(t,J=7.2Hz,2H), 3.83(s,3H), 4.01(br-t,2H), 7.40(d,J=8.8Hz,2H), 7.37(dd,J=7.6,5.6Hz,1H), 7.43(s,1H), 7.45(t,J=8.0Hz,1H), 7.49(d,J=7.6Hz,1H), 7.62(t,J=8.0Hz,1H), 7.76(d,J=8.0Hz,1H), 7.89(t,J=7.6Hz,1H), 8.10(d,J=8.8Hz,2H), 8.20(d,J=8.0Hz,1H), 8.54(dd,J=5.6,0.8Hz,1H).

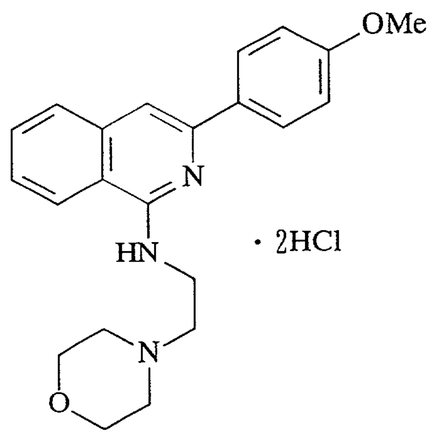
MS(FAB) m/z 356(M+H)$^+$

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 3.27(t,J=6.4Hz,2H), 3.88(s,3H), 4.11-4.16(m,2H), 6.40(br-t,1H), 6.99(d,J=8.8Hz,2H),

7.16(ddd,J=7.6,4.8,1.2Hz,1H), 7.23(d,J=7.6Hz,1H), 7.32(s,1H), 7.38(dt,J=8.0,1.2Hz,1H), 7.54(dt,J=8.0,1.2Hz,1H), 7.61(dt,J=7.6,2.0Hz,1H), 7.69(d,J=8.0Hz,1H), 7.75(d,J=8.0Hz,1H), 8.13(d,J=8.8Hz,2H), 8.62(dd,J=4.8,1.2Hz,1H).

Example 323 Synthesis of 1-[2-(4-morpholinyl)ethyl]amino-3-(4-methoxyphenyl)isoquinoline dihydrochloride



1-Chloro-3-(4-methoxyphenyl)isoquinoline (405 mg) and 4-(2-aminoethyl)morpholine (394 mg) were dissolved in N,N-dimethylformamide (5 ml), followed by the addition of potassium carbonate (415 ml), and the resulting mixture was stirred at 120°C overnight. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system). Then, the resulting product was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/isopropyl ether, to give the hydrochloride of the title compound as pale yellow

crystals (190 mg, yield; 27%).

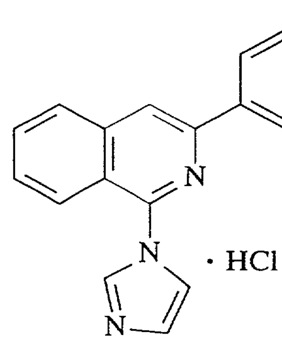
Hydrochloride:

m.p.; 135-136°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 3.28-3.52(2H,m), 3.48-3.56(2H,m), 3.81(3H,s), 3.84-3.94(4H,m), 4.06-4.16(4H,m), 7.05(2H,d,J=8.8Hz), 7.47(1H,s), 7.50-7.58(1H,m), 7.66-7.78(1H,m), 7.82(1H,d,J=8Hz), 7.94-8.06(2H,m), 8.40-8.58(1H,m).

ESI-Mass; 364(MH$^+$).

Example 324 Synthesis of 1-(1-imidazolyl)-3-(4-methoxyphenyl)isoquinoline hydrochloride



1-Chloro-3-(4-methoxyphenyl)isoquinoline (405 mg) and imidazole (204 mg) were dissolved in N,N-dimethylformamide (5 ml), followed by the addition of 60% sodium hydride (60 mg), and the resulting mixture was stirred at 80°C for 6 hr. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), and then the resulting product was

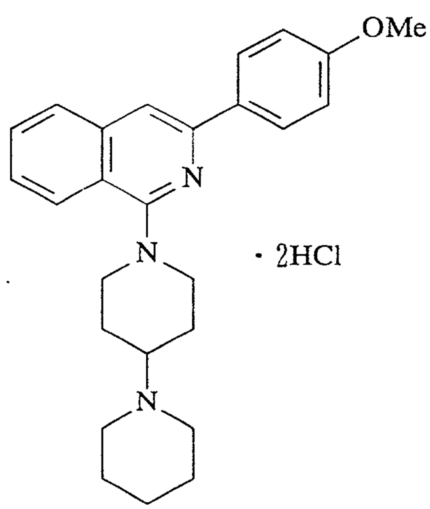
converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as a pale yellow amorphous (255 mg, yield; 53%).

Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 3.83(3H,s), 7.10(2H,d,J=8.8Hz), 7.90-7.96(2H,m), 8.00(1H,s), 8.17-8.23(3H,m), 8.40(1H,s), 8.69(1H,s), 9.80(1H,s).

ESI-Mass; 302(MH^+).

Example 325 Synthesis of 1-[4-(piperidin-1-yl)piperidin-1-yl]-3-(4-methoxyphenyl)isoquinoline dihydrohcloride



In the same manner as in Example 321, the hydrochloride of the title compound was obtained as yellow crystals (recrystallized in ethanol/isopropyl ether) (278 mg, yield; 40%) from 1-chloro-3-(4-methoxyphenyl)isoquinoline (405 mg) and 4-(piperidin-1-yl)piperidine (425 mg).

Hydrochloride:

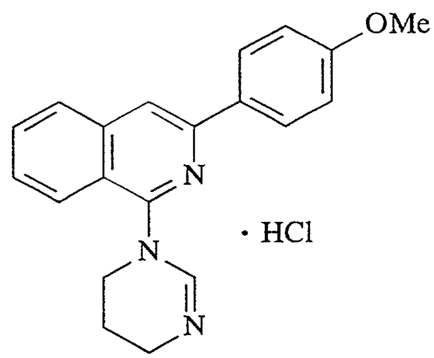
m.p.; 223-238°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.67-1.75(1H,m), 1.78-

1.86(4H,m), 1.97-2.09(2H,m), 2.19-2.26(2H,m), 2.90-3.08(5H,m), 3.36-3.50(3H,m), 3.80(3H,s), 3.96-4.04(2H,m), 7.04(2H,d,J=8.8Hz), 7.53(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.67(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.89(1H,s), 7.90(1H,d,J=8Hz), 8.01(1H,d,J=8Hz), 8.12(2H,d,J=8.8Hz).

ESI-Mass; 402(MH^+).

Example 326 Synthesis of 1-(1,4,5,6-tetrahydropyrimidin-1-yl)-3-(4-methoxyphenyl)isoquinoline hydrochloride



In the same manner as in Example 324, the hydrochloride of the title compound was obtained as a brown amorphous (80 mg, yield; 13%) from 1-chloro-3-(4-methoxyphenyl)isoquinoline (405 mg) and 1,4,5,6-tetrahydropyrimidine (370 mg).

Hydrochloride:

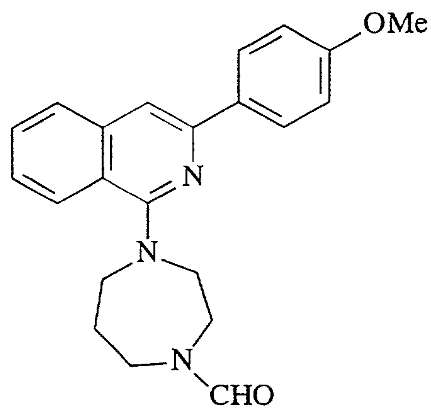
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 2.24(2H,qui,J=5.6Hz), 3.58(2H,t,J=5.6Hz), 4.15(2H,t,J=5.6Hz), 7.09(2H,d,J=8.8Hz), 7.74(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.88(1H,ddd,J=8Hz,7Hz,1.2Hz), 8.11(1H,d,J=8Hz), 8.13(1H,d,J=8Hz), 8.16(2H,d,J=8.8Hz), 8.50(1H,s), 8.91(1H,d,J=6Hz), 11.02(1H,br-s).

ESI-Mass; 318(MH^+).

Example 327 Synthesis of 1-(1-ethylhomopiperazin-4-yl)-3-

(4-methoxyphenyl)isoquinoline dihydrochloride

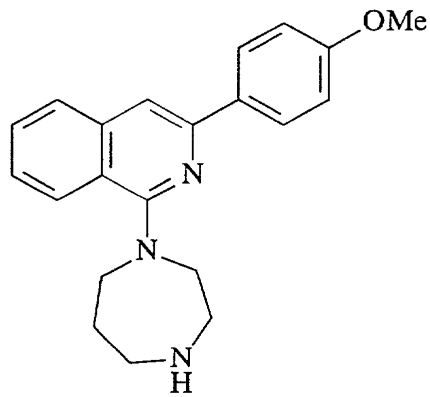
(327-1) 1-(1-Formylhomopiperazin-4-yl)-3-(4-methoxyphenyl)isoquinoline



In the same manner as in Example 2, the title compound was obtained as a brown oil (3.173 g, yield; 68%) from 1-chloro-3-(4-methoxyphenyl)isoquinoline (3.506 g) and 1-formylhomopiperazine (5 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 2.06-2.16(2H,m), 3.59(1H,t,J=6Hz), 3.67-3.98(5H,m), 3.85(3H,s), 3.83-3.91(2H,m), 6.99(1H,d,J=8.8Hz), 7.00(1H,d,J=8.8Hz), 7.41(0.5H,ddd,J=8Hz,7Hz,1.2Hz), 7.42(0.5H,ddd,J=8Hz,7Hz,1.2Hz), 7.55(0.5H,ddd,J=8Hz,7Hz,1.2Hz), 7.56(0.5H,ddd,J=8Hz,7Hz,1.2Hz), 7.58(1H,s), 7.74(1H,d,J=8Hz), 7.99(0.5H,d,J=8Hz), 8.00(0.5H,d,J=8Hz), 8.05(1H,d,J=8.8Hz), 8.06(1H,d,J=8.8Hz), 8.14(0.5H,s), 8.18(0.5H,s).

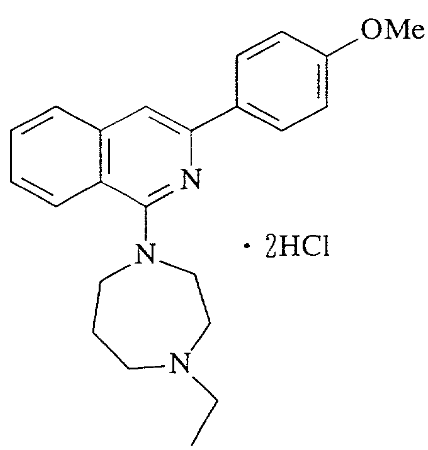
(327-2) 1-(1-Homopiperazinyl)-3-(4-methoxyphenyl)isoquinoline



In the same manner as in Example 236, the title compound was obtained as a pale yellow solid (2.467 g, yield; 84%) from 1-(1-formylhomopiperazin-4-yl)-3-(4-methoxyphenyl)isoquinoline (3.173 g).

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 2.01-2.08(2H,m), 3.09(2H,t,J=5.8Hz), 3.20-3.23(2H,m), 3.85-3.90(7H,m), 7.00(2H,d,J=8.8Hz), 7.39(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.53(1H,s), 7.55(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.74(1H,d,J=8Hz), 8.10(2H,d,J=8.8Hz).

(327-3) 1-(1-Ethylhomopiperazin-4-yl)-3-(4-methoxyphenyl)isoquinoline hydrochloride



In the same manner as in Example 236, the hydrochloride

of the title compound was obtained as yellow crystals (recrystallized from ethanol/isopropyl ether) (228 mg, yield; 82%) from 1-(1-homopiperazinyl)-3-(4-methoxyphenyl)isoquinoline (355 mg) and 1-bromoethane (87 ml).

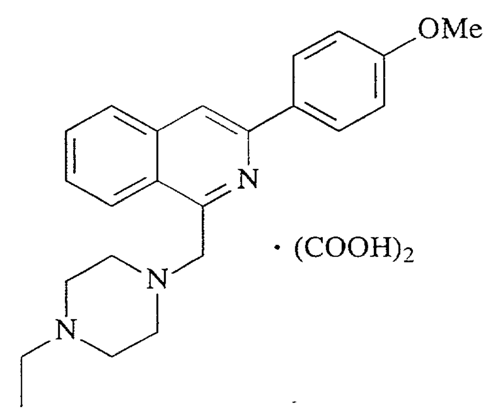
Hydrochloride:

m.p.; 124-125°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.28(3H,t,J=7.2Hz), 2.15-2.25(1H,m), 2.30-2.45(1H,m), 3.15-3.28(3H,m), 3.50-3.60(2H,m), 3.68-3.78(2H,m), 3.80(3H,s), 3.90-4.08(2H,m), 4.10-4.18(1H,m), 7.03(2H,d,J=8.8Hz), 7.48(1H,ddd,J=8.4Hz,7Hz,1.2Hz), 7.65(1H,ddd,J=8.4Hz,7Hz,1.2Hz), 7.80(1H,s), 7.87(1H,d,J=8.4Hz), 8.04(1H,d,J=8.4Hz), 8.10(1H,d,J=8.8Hz), 10.62(1H,br-s).

ESI-Mass; 362(MH^+).

<u>Example 328</u> <u>Synthesis of 3-(4-methoxyphenyl)-1-(4-ethylpiperazin-1-yl)methylisoquinoline oxalate</u>



3-(4-Methoxyphenyl)-1-chloroisoquinoline (3.25 g) was dissolved in tetrahydrofuran (30 ml), followed by the addition

of 3.0M ethylmagnesium bromide diethyl ether solution (12 ml) and $NiCl_2$ (dppp) (50 mg) at $0^{\circ}C$. After the mixture was reacted overnight at room temperature, the resulting reaction solution was poured into an aqueous solution of saturated ammonium chloride and extracted with ethyl acetate. The resulting organic layer was washed with water and brine, dried and evaporated, to give 3-(4-methoxyphenyl)-1-methylisoquinoline as an oil (3.3 g, yield; 100%).

To the resulting oil (3.3 g) were added chloroform (30 ml) and m-chloroperbenzoic acid (MCPBA, 4.4 g) under ice-cooling, and the mixture was reacted at room temperature for 1 hr. To the resulting reaction solution was added a 2N aqueous solution of sodium hydroxide, and the mixture was stirred 10 min, and then extracted with ethyl acetate. The resulting organic layer was washed with water and brine, dried and then purified by NH-silica gel column chromatography (hexane/ethyl acetate system), to give 3-(4-methoxyphenyl)-1-methylisoquinoline N-oxide as a yellow oil (2.42 g, yield; 76%).

To the resulting oil (2.4 g) were added chloroform (10 ml) and p-toluenesulfonyl chloride (1.9 g), and the mixture was reacted at $50^{\circ}C$ overnight. To the reaction solution was added an aqueous solution of saturated sodium bicarbonate, and the mixture was stirred for 10 min and then extracted with ethyl acetate. The resulting organic layer was washed with water and brine, dried and purified by silica gel column chromatography (hexane/ethyl acetate system), to give 3-(4-methoxyphenyl)-

1-chloromethylisoquinoline (783 mg, yield; 30%).

In the same manner as in Example 1, the title compound was obtained (995 mg, yield; 99%) from 3-(4-methoxyphenyl)-1-chloromethylisoquinoline (783 mg) and ethylpiperazine (0.57 ml).

The resulting compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 219-221°C

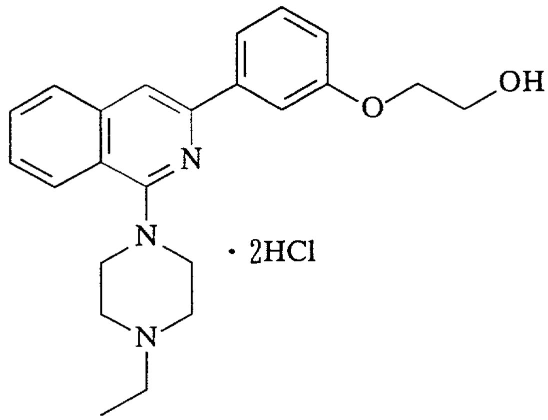
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.87(br,4H), 3.04(q,J=7.2Hz,2H), 3.14(br,4H), 3.84(s,3H), 4.26(s,2H), 7.09(d,J=8.8Hz,2H), 7.62(dt,J=8.4,1.2Hz,1H), 7.76(dt,J=8.4,1.2Hz,1H), 8.01(d,J=8.4Hz,1H), 8.19(d,J=8.8Hz,2H), 8.28(s,1H), 8.43(d,J=8.4Hz,1H).

MS(FAB) m/z 362$(M+H)^+$.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.08(t,J=7.2Hz,3H), 2.42(q,J=7.2Hz,2H), 2.50(br,4H), 2.72(br,4H), 3.88(s,3H), 4.20(s,2H), 7.03(d,J=8.8Hz,2H), 7.52(t,J=8.4Hz,1H), 7.63(t,J=8.4Hz,1H), 7.82(d,J=8.4Hz,1H), 7.90(s,1H), 8.11(d,J=8.8Hz,2H), 8.45(d,J=8.4Hz,1H).

Example 329 Synthesis of 1-(4-Ethylpiperazin-1-yl)-3-[3-(2-hydroxyethoxy)phenyl]isoquinoline dihydrochloride



According to the methods of Examples 10-1 and 10-2, 1-(4-ethylpiperazin-1-yl)-3-[2-(t-butyldimethylsilyloxy)ethoxy]phenylisoquinoline (0.59 g) was obtained from N-methyl-2-methylbenzamide (5.97 g) and 3-methoxybenzonitrile (5.33 g).

The resulting 1-(4-ethylpiperazin-1-yl)-3-[2-(t-butyldimethylsilyloxy)ethoxy]phenylisoquinoline (0.58 g) was dissolved in tetrahydrofuran (5 ml), to which was then added 1.0M tetrabutylammonium fluoride/tetrahydrofuran solution (1.42 ml), and the mixture was stirred for 7.5 hr. The solvent was evaporated, and the resulting residue was dissolved in ethyl acetate. The resulting solution was washed with water (four times) and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.32 g of the free compound of the title compound as a pale yellow oil.

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized

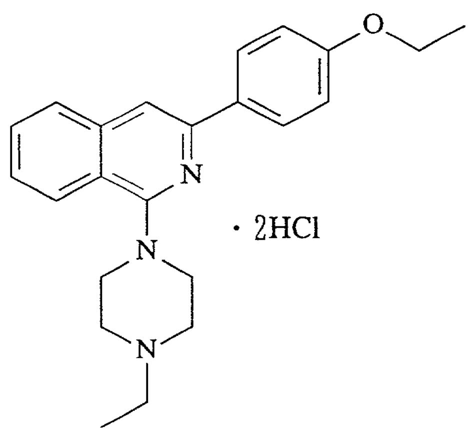
from ethanol/ether, to give 0.34 g of the title compound as a yellow powder.

Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.77(br-t,4H), 3.59(br-t,4H), 4.02(t,J=4.5Hz,2H), 4.20(t,J=4.5Hz,2H), 6.94(dd,J=2.6,8.2Hz,1H), 7.38(t,J=8.0Hz,1H), 7.47(br-t,1H), 7.59(br-t,1H), 7.70(s,1H), 7.75(br-d,1H), 7.79(d,J=8.0Hz,1H), 7.82(br-t,1H), 8.08(d,J=8.4Hz,1H).

MS(FAB) m/z 378(M+H)$^+$.

<u>Example 330 Synthesis of 1-(4-Ethylpiperazin-1-yl)-3-(4-ethoxyphenyl)isoquinoline dihydrochloride</u>



According to the method of Example 7, 1-(4-ethylpiperazin-1-yl)-3-(4-hydroxyphenyl)isoquinoline was obtained.

Sodium hydride (0.04 g) was washed with n-hexane, suspended in N,N-dimethylformamide (2 ml) and stirred under ice-cooling. The resulting 1-(4-ethylpiperazin-1-yl)-3-(4-hydroxyphenyl)isoquinoline (0.25 g) described above was added

thereto, and the mixture was stirred at room temperature for 35 min. The mixture was again ice-cooled, followed by the addition of ethyl iodide (90 ml), and the mixture was stirred in nitrogen atmosphere at 50°C for 1.5 hr. Water was added to the reaction solution, and then extracted with ethyl acetate. The resulting extract was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.22 g of the free compound of the title compound as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 1.44(t,J=7.0Hz,3H), 2.54(q,J=7.2Hz,2H), 2.74(br-t,4H), 3.58(br-t,4H), 4.08(q,J=7.0Hz,2H), 6.98(d,J=8.8Hz,2H), 7.41(br-t,1H), 7.54(br-t,1H), 7.60(s,1H), 7.74(d,J=8.0Hz,1H), 8.05(d,J=8.4Hz,1H), 8.11(d,J=8.8Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/ether, to give the title compound as a yellow powder.

Hydrochloride:

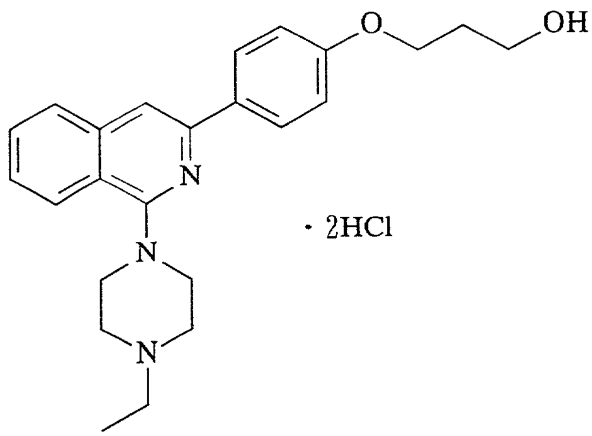
m.p.; 197-198°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 1.37(t,J=6.8Hz,3H), 3.20-3.27(m,2H), 3.31-3.39(m,2H), 3.51(br-t,2H), 3.62(br-d,2H), 3.98(br-d,2H), 4.10(q,J=6.8Hz,2H), 7.05(d,J=9.2Hz,2H), 7.57(br-t,1H),

7.72(br-t,1H), 7.95(d,J=8.0Hz,1H), 7.99(s,1H), 8.10(d,J=8.4Hz,1H), 8.14(d,J=9.2Hz,2H), 10.86(br-s,1H).

MS(FAB) m/z 362$(M+H)^+$.

Example 331 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxypropoxy)phenyl]isoquinoline dihydrochloride



According to the method of Example 7, 1-(4-ethylpiperazin-1-yl)-3-(4-hydroxyphenyl)isoquinoline was obtained.

Sodium hydride (0.08 g) was washed with n-hexane, suspended in N,N-dimethylformamide (4 ml) and stirred under ice-cooling. The resulting 1-(4-ethylpiperazin-1-yl)-3-(4-hydroxyphenyl)isoquinoline (0.49 g) described above was added thereto, and the mixture was stirred at room temperature for 25 min. The mixture was again ice-cooled, followed by the addition of 3-(tetrahydropyranyloxy)propyl bromide (0.50 g), and the mixture was stirred in nitrogen atmosphere at 50°C overnight. Water was added to the reaction solution, and then extracted with ethyl acetate. The resulting extract was washed with water and brine, and dried over magnesium sulfate. The

solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.66 g of the tetrahydropyranyl-protected compound of the titled compound as a pale yellow oil.

Methanol (5 ml) and 2N hydrochloric acid (5 ml) were added to the protected compound (0.65 g) described above, and the mixture was left as it was at room temperature for 1.5 hr. The solvent was evaporated, and then a 5N aqueous solution of sodium hydroxide was added to the resulting residue. The mixture was extracted with ethyl acetate. The resulting extract was washed with brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.43 g of the free compound of the title compound as a pale yellow oil.

Free form:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.4Hz,3H), 2.08(quintet,J=6.0Hz,2H), 2.56(q,J=7.4Hz,2H), 2.76(br-t,4H), 3.58(br-t,4H), 3.90(t,J=6.0Hz,2H), 4.20(t,J=6.0Hz,2H), 7.00(d,J=8.8Hz,2H), 7.43(br-t,1H), 7.56(br-t,1H), 7.61(s,1H), 7.76(d,J=7.6Hz,1H), 8.06(d,J=8.4Hz,1H), 8.12(d,J=8.8Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/IPE, to give the title compound as a yellow powder.

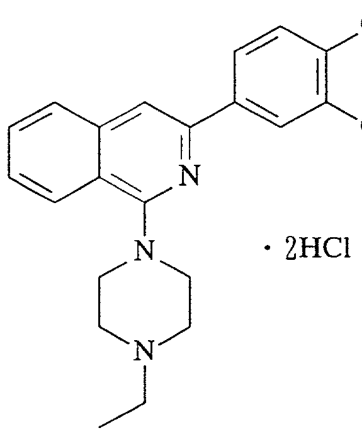
Hydrochloride:

m.p.; 112-113°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.32(t,J=7.4Hz,3H), 1.90(quintet,J=6.2Hz,2H), 3.22-3.28(m,2H), 3.34-3.48(m,4H), 3.59(t,J=6.2Hz,2H), 3.64(br-d,2H), 4.00(br-d,2H), 4.11(t,J=6.2Hz,2H), 7.06(d,J=8.8Hz,2H), 7.57(br-t,1H), 7.72(br-t,1H), 7.95(d,J=8.4Hz,1H), 8.00(s,1H), 8.10(d,J=8.0Hz,1H), 8.14(d,J=8.8Hz,2H), 10.37(br-s,1H).

MS(FAB) m/z 392(M+H)$^+$.

Example 332 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(3,4-ethylenedioxyphenyl)isoquinoline dihydrochloride



According to the method of Example 10-1, N-methyl-2-methylbenzamide (5.97 g) and 3,4-ethylenedioxybenzonitrile (6.41 g) were reacted, to give 3-(3,4-ethylenedioxyphenyl)isoquinolin-1-one (3.58 g).

The resulting 3-(3,4-ethylenedioxyphenyl)isoquinolin-1-one (1.94 g) was reacted with phosphorus oxychloride (20 ml) according to the method of Example 10-2, to give 1-chloro-3-(3,4-ethylenedioxyphenyl)isoquinoline. The resulting compound was reacted, as it was, with N-ethylpiperazine (6 ml) at 100°C overnight. The reaction solution was evaporated, and

to the resulting residue were added ethyl acetate and purified water. The resulting ethyl acetate layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 1.63 g of the free compound of the title compound as a pale yellow oil.

Free form:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.75(br-t,4H), 3.57(br-t,4H), 4.32(s,4H), 6.95(d,J=8.4Hz,1H), 7.43(br-t,1H), 7.56(br-t,1H), 7.59(s,1H), 7.66(dd,J=0.8,8.4Hz,1H), 7.74-7.77(m,1H), 8.05(d,J=8.0Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/IPE, to give the title compound as a yellow powder.

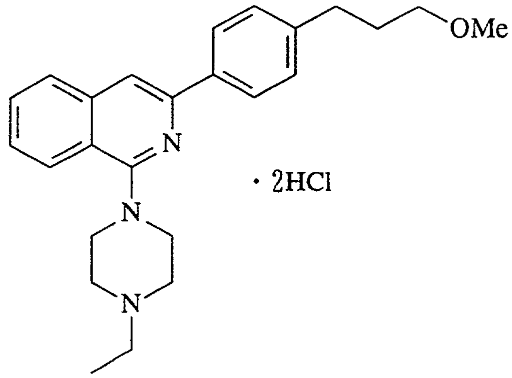
Hydrochloride:

m.p.; 141-143°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,,3H), 3.20-3.26(m,2H), 3.30-3.37(m,2H), 3.51(br-t,2H), 3.62(br-d,2H), 3.97(br-d,2H), 4.30(s,4H), 6.98(d,J=8.4Hz,1H), 7.58(br-t,1H), 7.68-7.74(m,3H), 7.95(d,J=8.0Hz,1H), 7.99(s,1H), 8.09(d,J=8.4Hz,1H), 11.01(s,1H).

MS(FAB) m/z 376$(M+H)^+$.

Example 333 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(3-methoxypropyl)phenyl]isoquinoline dihydrochloride



According to the method of Example 10-1, N-methyl-2-methylbenzamide (3.75 g) and 4-(3-methoxypropyl)benzonitrile (4.40 g) were reacted, to give 3-[4-(3-methoxypropyl)phenyl]isoquinolin-1-one (1.98 g).

The resulting 3-[4-(3-methoxypropyl)phenyl]isoquinolin-1-one (1.85 g) was reacted with phosphorus oxychloride (20 ml) according to the method of Example 10-2, to give 1-chloro-3-[4-(3-methoxypropyl)phenyl]isoquinoline. The resulting compound was reacted, as it was, with N-ethylpiperazine (6 ml) at 100°C overnight. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and purified water. The resulting ethyl acetate layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.63 g of the free compound of the title compound as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.15(t,J=7.2Hz,3H), 1.88-

1.95(m,2H), 2.52(q,J=7.2Hz,2H), 2.71-2.74(m,6H), 3.33(s,3H), 3.39(t,J=6.4Hz,2H), 3.56(br-t,4H), 7.27(d,J=8.0Hz,2H), 7.41(br-t,1H), 7.53(br-t,1H), 7.64(s,1H), 7.73(d,J=8.0Hz,1H), 8.04(d,J=8.0Hz,1H), 8.08(d,J=8.0Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/IPE, to give the free compound of the title compound as a yellow powder.

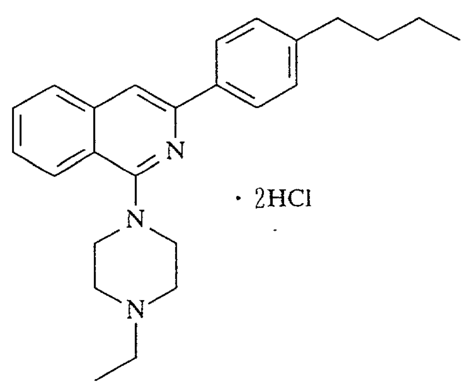
Hydrochloride:

m.p.; 191-192°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.06(t,J=7.2Hz,3H), 1.33(t,J=7.4Hz,3H), 1.81-1.88(m,2H), 2.68(br-t,2H), 3.19-3.25(m,2H), 3.25(s,3H), 3.30-3.38(m,2H), 3.35(t,J=6.4Hz,2H), 3.54(br-t,2H), 3.62(br-d,2H), 3.99(br-d,2H), 7.34(d,J=8.4Hz,2H), 7.60(br-t,1H), 7.74(br-t,1H), 7.98(d,J=8.0Hz,1H), 8.06(s,1H), 8.11-8.13(m,3H), 11.09(br-s,1H).

MS(FAB) m/z 390(M+H)$^+$.

<u>Example 334 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(n-butyl)phenyl]isoquinoline dihydrochloride</u>



According to the method of Example 10-1, N-methyl-2-methylbenzamide (4.28 g) and 4-(n-butyl)benzonitrile (4.57 g) were reacted, to give 3-[4-(n-butyl)phenyl]isoquinolin-1-one (2.51 g).

The resulting 3-[4-(n-butyl)phenyl]isoquinolin-1-one (2.44 g) was reacted with phosphorus oxychloride (20 ml) according to the method of Example 10-2, to give 1-chloro-3-[4-(n-butyl)phenyl]isoquinoline. The resulting compound was reacted, as it was, with N-ethylpiperazine (11 ml) at 100°C overnight. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and purified water. The resulting ethyl acetate layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 1.78 g of the free compound of the title compound as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.95(t,J=7.2Hz,3H), 1.18(t,J=7.2Hz,3H), 1.35-1.44(m,2H), 1.61-1.68(m,2H), 2.55(q,J=7.2Hz,2H), 2.67(t,J=7.8Hz,2H), 2.76(br-t,4H), 3.59(br-t,4H), 7.28(d,J=8.4Hz,2H), 7.44(br-t,1H), 7.57(br-t,1H), 7.67(s,1H), 7.78(d,J=8.0Hz,1H), 8.06-8.09(m,3H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/IPE, to give the title compound as a yellow powder.

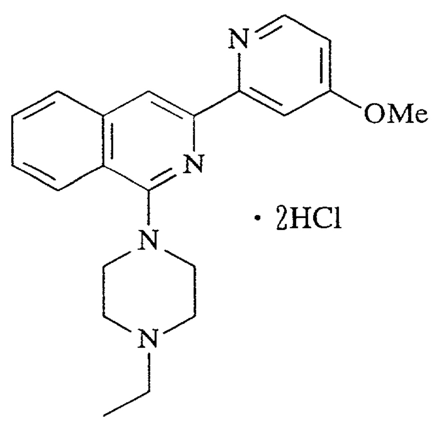
Hydrochloride:

m.p.; 190-192°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.92(t,J=7.4Hz,3H), 1.29-1.39(m,5H), 1.56-1.64(m,2H), 2.64(t,J=7.6Hz,2H), 3.19-3.26(m,2H), 3.30-3.39(m,2H), 3.54-3.63(m,4H), 3.98(br-d,2H), 7.33(d,J=8.4Hz,2H), 7.60(br-t,1H), 7.74(br-t,1H), 7.98(d,J=8.0Hz,1H), 8.05(s,1H), 8.11(d,J=8.4Hz,2H), 11.33(br-s,1H).

MS(FAB) m/z 374(M+H)$^+$.

Example 335 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(4-methoxypyridin-2-yl)isoquinoline dihydrochloride



According to the method of Example 10-1, N-methyl-2-methylbenzamide (4.96 g) and 2-cyano-4-methoxypyridine (4.46 g) were reacted, to give 3-(4-methoxypyridin-2-yl)isoquinolin-1-one (2.51 g).

The resulting 3-(4-methoxypyridin-2-yl)isoquinolin-1-one (0.85 g) was reacted with phosphorus oxychloride (10 ml) according to the method of Example 10-2, to give 1-chloro-3-(4-methoxypyridin-2-yl)isoquinoline. The resulting

compound was reacted, as it was, with N-ethylpiperazine (2.5 ml) at 100°C overnight. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and purified water. The resulting ethyl acetate layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.40 g of the free compound of the title compound as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.77(br-t,4H), 3.58(br-t,4H), 3.95(s,3H), 6.80(dd,J=2.6,5.6Hz,1H), 7.50(br-t,1H), 7.60(br-t,1H), 7.88(d,J=8.0Hz,1H), 8.11(d,J=8.4Hz,1H), 8.12(d,J=2.6Hz,1H), 8.40(s,1H), 8.51(d,J=5.6Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/IPE, to give the title compound as a yellow powder.

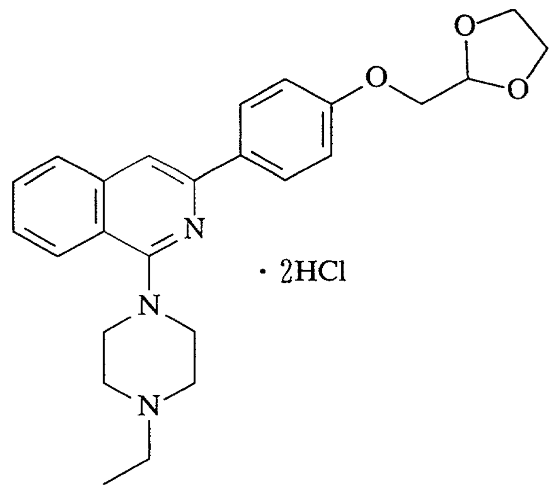
Hydrochloride:

m.p.; 172-173°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 3.20-3.26(m,2H), 3.32-3.40(m,2H), 3.59-3.68(m,4H), 4.18(s,3H), 4.22(br-d,2H), 7.50(br-d,1H), 7.80(br-t,1H), 7.90(br-t,1H), 8.09(d,J=7.6Hz,1H), 8.22(d,J=8.4Hz,1H), 8.26(d,J=2.0Hz,1H), 8.73(s,1H), 8.77(d,J=6.8Hz,1H), 11.36(br-s,1H).

MS(FAB) m/z 349(M+H)$^+$.

Example 336 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(1,3-dioxolan-2-ylmethyloxy)phenyl]isoquinoline



According to the method of Example 7, 1-(4-ethylpiperazin-1-yl)-3-(4-hydroxyphenyl)isoquinoline was prepared.

The resulting 1-(4-ethylpiperazin-1-yl)-3-(4-hydroxyphenyl)isoquinoline (0.53 g) was dissolved in N,N-dimethylformamide (5 ml), to which were added potassium carbonate (0.24 g) and 2-bromomethyl-1,3-dioxolane (250 ml), and the mixture was stirred at 90°C overnight. Water was added to the reaction solution, and then the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.47 g of the title compound as a pale yellow oil.

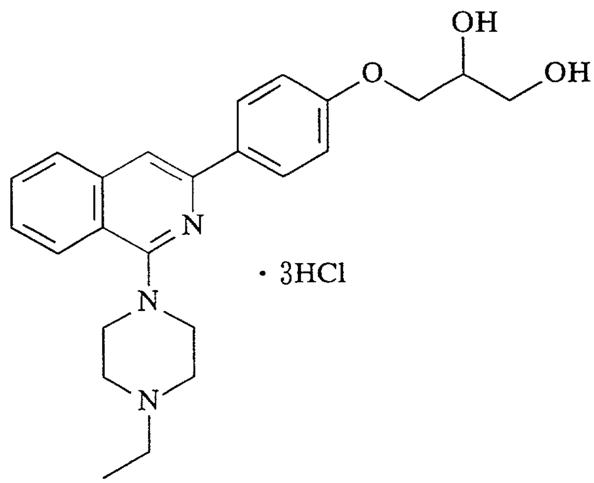
Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.4Hz,3H),

2.55(q,J=7.4Hz,2H), 2.75(br-t,4H), 3.58(br-t,4H), 3.97-4.10(m,4H), 4.11(d,J=4.0Hz,2H), 5.33(t,J=4.0Hz,1H), 7.03(d,J=8.6Hz,2H), 7.43(br-t,1H), 7.56(br-t,1H), 7.61(s,1H), 7.76(d,J=7.6Hz,1H), 8.06(d,J=8.4Hz,1H), 8.11(d,J=8.6Hz,2H).

MS(FAB) m/z 420(M+H)$^+$.

Example 337 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(2,3-dihydroxypropoxy)phenyl]isoquinoline dihydrochloride



According to the method of Example 7, 1-(4-ethylpiperazin-1-yl)-3-(4-hydroxyphenyl)isoquinoline was prepared.

Sodium hydride (0.07 g) was washed with n-hexane, suspended in N,N-dimethylformamide (0.5 ml) and stirred under ice-cooling, to which was then added the resulting 1-(4-ethylpiperazin-1-yl)-3-(4-hydroxyphenyl)isoquinoline (0.52 g) dissolved in N,N-dimethylformamide (5 ml), and the mixture was stirred at room temperature for 20 min. The mixture was again ice-cooled, followed by the addition of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl tosylate (0.67 g), and the

mixture was stirred overnight in nitrogen atmosphere at 50°C. Water was added to the reaction solution, followed by the extraction with ethyl acetate. The extract was washed with water and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.55 g of the acetonide-protected compound of the title compound as a pale yellow oil.

2N Hydrochloric acid (25 ml) was added to the above-mentioned protected compound (0.53 g) to dissolve, and the mixture was then left to stand at room temperature for 1 hr. A 8N aqueous solution of sodium hydroxide was added thereto, and the resulting solution was extracted with ethyl acetate. The extract was washed with a 10% aqueous solution of sodium carbonate and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give the free compound of the title compound as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.76(br-t,4H), 3.58(br-t,4H), 3.79(dd,J=5.2,11.6Hz,1H), 3.88(dd,J=4.0,11.6Hz,1H), 4.10-4.18(m,3H), 7.01(d,J=9.2Hz,2H), 7.44(br-t,1H), 7.57(br-t,1H), 7.62(s,1H), 7.77(d,J=8.0Hz,1H), 8.06(d,J=8.4Hz,1H), 8.25(d,J=9.2Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/IPE, to give 0.26 g of the title compound as a yellow powder.

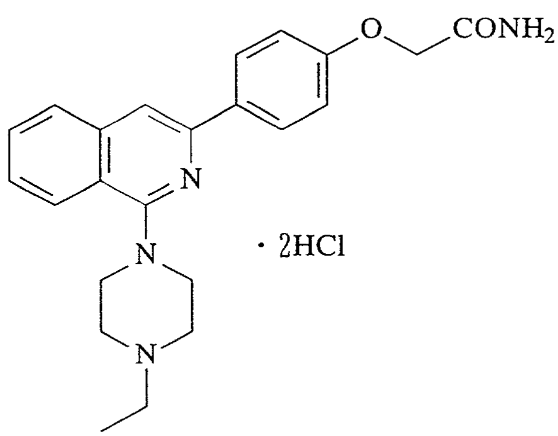
Hydrochloride:

m.p.; 133-135°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.47(t,J=7.2Hz,3H), 3.36-3.41(m,2H), 3.52-3.58(m,2H), 3.66-3.82(m,6H), 3.99-4.09(m,2H), 4.16(dd,J=4.4,9.6Hz,1H), 4.29(br-d,2H), 7.13(d,J=8.8Hz,2H), 7.71(br-t,1H), 7.86(br-t,1H), 7.88(s,1H), 7.97(d,J=8.8Hz,2H), 8.01(d,J=8.0Hz,1H), 8.24(d,J=8.4Hz,1H), 10.79(br-s,1H).

MS(FAB) m/z 408$(M+H)^+$.

Example 338 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(4-carbamoylmethoxyphenyl)isoquinoline dihydrochloride



According to the method of Example 7, 1-(4-ethylpiperazin-1-yl)-3-(4-hydroxyphenyl)isoquinoline was prepared.

The resulting 1-(4-ethylpiperazin-1-yl)-3-(4-

hydroxyphenyl)isoquinoline (0.57 g) was dissolved in N,N-dimethylformamide (5 ml), to which were added potassium carbonate (0.24 g) and ethyl bromoacetate (210 ml), and the mixture was stirred at room temperature for 2 days. Water was added to the reaction solution, followed by the extraction with ethyl acetate. The extract was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give obtain 1-(4-ethylpiperazin-1-yl)-3-[4-(ethoxycarbonylmethoxy)phenyl]isoquinoline (0.57 g) as a pale yellow viscous oil.

To the resulting 1-(4-ethylpiperazin-1-yl)-3-[4-(ethoxycarbonylmethoxy)phenyl]isoquinoline (0.55 g) was added a solution of 10% ammonia/ethanol (20 ml) for dissolution, and the mixture was sealed and left to stand at room temperature for 2 days. The solvent was evaporated, and the resulting residue was purified by recrystallization (chloroform/n-hexane system), to give 0.47 g of the free compound of the title compound as a colorless powder.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.76(br-t,4H), 3.59(br-t,4H), 4.58(s,2H), 5.64(br-s,1H), 6.59(br-s,1H), 7.03(d,J=8.8Hz,2H), 7.45(br-t,1H), 7.58(br-t,1H), 7.63(s,1H), 7.78(d,J=8.0Hz,1H), 8.07(d,J=8.4Hz,1H), 8.15(d,J=8.8Hz,2H).

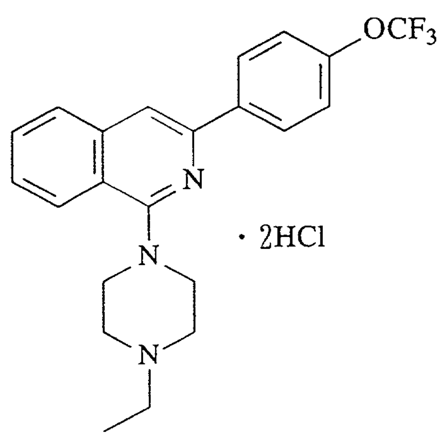
The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/IPE, to give the title compound (0.26 g) as a yellow powder.

Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 3.20-3.27(m,2H), 3.31-3.39(m,2H), 3.50(br-t,2H), 3.62(br-d,2H), 4.00(br-d,2H), 4.51(s,2H), 7.09(d,J=9.0Hz,2H), 7.44(br-s,1H), 7.56-7.60(m,2H), 7.73(br-t,1H), 7.96(d,J=8.0Hz,1H), 8.01(s,1H), 8.10(d,J=8.4Hz,1H), 8.16(d,J=9.0Hz,2H), 10.78(br-s,1H).

MS(FAB) m/z 391(M+H)$^+$.

<u>Example 339 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(4-trifluoromethoxyphenyl)isoquinoline dihydrochloride</u>



According to the method of Example 10-1, N-methyl-2-methylbenzamide (5.97 g) and 4-trifluoromethoxybenzonitrile (7.49 g) were reacted, to give 3-(4-trifluoromethoxyphenyl)isoquinolin-1-one (3.04 g).

The resulting 3-(4-

trifluoromethoxyphenyl)isoquinolin-1-one (3.01 g) was reacted with phosphorus oxychloride (20 ml) according to the method of Example 10-2, to give 1-chloro-3-(4-trifluoromethoxyphenyl)isoquinoline, which was then reacted as it was with N-ethylpiperazine (40 ml) at 90°C overnight. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and purified water. The ethyl acetate layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 3.65 g of the free compound of the title compound as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.4Hz,3H), 2.56(q,J=7.4Hz,2H), 2.76(br-t,4H), 3.59(br-t,4H), 7.31(d,J=8.8Hz,2H), 7.48(br-t,1H), 7.60(br-t,1H), 7.67(s,1H), 7.80(d,J=7.6Hz,1H), 8.08(d,J=8.4Hz,1H), 8.19(d,J=8.8Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/ether, to give the title compound as a yellow powder.

Hydrochloride:

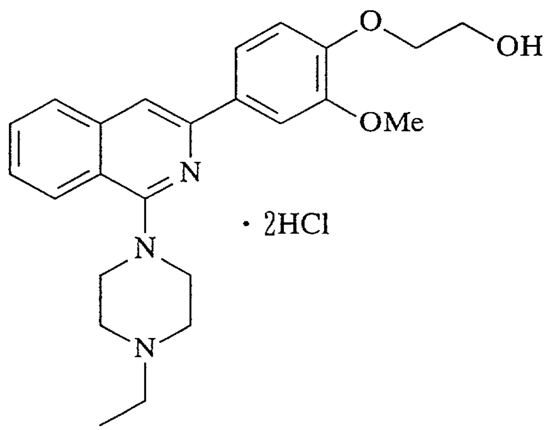
m.p.; 113-115°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.35(t,J=7.4Hz,3H), 3.19-3.26(m,2H), 3.30-3.39(m,2H), 3.56-3.63(m,4H), 4.01(br-d,2H), 7.51(d,J=8.4Hz,2H), 7.64(br-t,1H), 7.77(br-t,1H),

8.01(d,J=8.4Hz,1H), 8.14(br-d,1H), 8.15(s,1H), 8.33(d,J=8.4Hz,2H), 11.45(br-s,1H).

MS(FAB) m/z 402$(M+H)^+$.

<u>Example 340</u> <u>Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxyethoxy)-3-methoxyphenyl]isoquinoline dihydrochloride</u>



According to the method of Example 10-1, N-methyl-2-methylbenzamide (5.97 g) and 4-(2-benzyloxyethoxy)-3-methoxybenzonitrile (9.57 g) were reacted, to give 3-[4-(2-benzyloxyethoxy)-3-methoxyphenyl]isoquinolin-1-one (3.20 g).

The resulting 3-[4-(2-benzyloxyethoxy)-3-methoxyphenyl]isoquinolin-1-one (3.15 g) was reacted with phosphorus oxychloride (20 ml) according to the method of Example 10-2, to give 3-[4-(2-benzyloxyethoxy)-3-methoxyphenyl)-2-chloroisoquinoline. Then, N-ethylpiperazine (30 ml) and potassium carbonate (1.83 g) were added to the resulting compound as it was. The resulting mixture was reacted at 90°C overnight. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and purified water. The ethyl acetate layer was washed

with water and brine, and dried over magnesium sulfate. The solvent was evaporated, to give 3-[4-(2-benzyloxyethoxy)-3-methoxyphenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline.

The resulting compound was dissolved in methanol (100 ml), followed by the addition of 10% palladium/carbon catalyst (0.50 g), and then the overnight catalytic reduction was conducted at atmospheric pressure. The catalyst was filtered off, and the solvent was evaporated. Water was added to the resulting residue, to which was then added sodium carbonate to adjust the resulting solution to pH 8, to give 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxyethoxy)-3-methoxyphenyl]isoquinoline as an insoluble matter. The filtrate was extracted with ethyl acetate, washed with brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxyethoxy)-3-methoxyphenyl]isoquinoline was combined with the same compound previously collected by filtration, recrystallized from chloroform/n-hexane, to give 1.20 g of the free compound of the title compound as a colorless powder.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.77(br-s,4H), 3.58(br-s,4H), 3.97(t,J=4.4Hz,2H), 4.00(s,3H), 4.20(t,J=4.4Hz,2H), 7.03(d,J=8.4Hz,1H), 7.45(br-t,1H), 7.59(br-t,1H), 7.64(s,1H), 7.69(dd,J=2.0,8.4Hz,1H), 7.78(d,J=8.0Hz,1H), 7.86(d,J=2.0Hz,1H), 8.08(d,J=8.0Hz,1H).

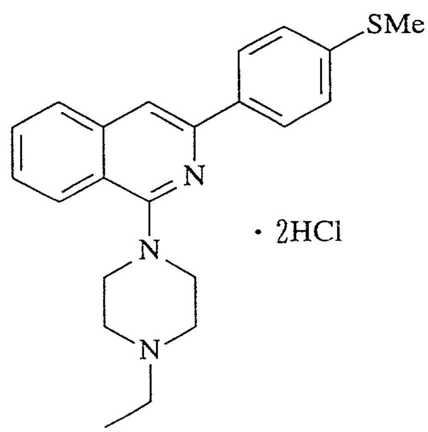
The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/IPE, to give the title compound as a yellow powder.

m.p.: 128-129°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.4Hz,3H), 3.20-3.26(m,2H), 3.31-3.39(m,2H), 3.53(br-t,2H), 3.63(br-d,2H), 3.76(t,J=5.2Hz,2H), 3.90(s,3H), 4.00(br-d,2H), 4.05(t,J=5.2Hz,2H), 7.09(d,J=8.4Hz,1H), 7.58(br-t,1H), 7.73(br-t,1H), 7.76-7.80(m,2H), 7.96(d,J=8.4Hz,1H), 8.04(s,1H), 8.10(d,J=8.0Hz,1H), 10.95(br-s,1H).

MS(FAB) m/z 408(M+H)$^+$.

<u>Example 341</u> <u>Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(4-methylthiophenyl)isoquinoline dihdyrochloride</u>



According to the method of Example 10-1, N-methyl-2-methylbenzamide (5.97 g) and 4-cyanothioanisole (5.97 g) were reacted, to give 3-(4-methylthiophenyl)isoquinolin-1-one (5.00 g).

The resulting 3-(4-methylthiophenyl)isoquinolin-1-one (0.73 g) was reacted with phosphorus oxychloride (5 ml)

according to the method of Example 10-2, to give 1-chloro-3-(4-methylthiophenyl)isoquinoline. Then, N-ethylpiperazine (10 ml) and potassium carbonate (0.36 g) were added to the resulting product as it was. The resulting mixture were reacted at 100°C overnight. The reaction solution was evaporated, and the resulting residue were added ethyl acetate and purified water. The ethyl acetate layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.95 g of the free compound of the title compound as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.54(s,3H), 2.56(q,J=7.2Hz,2H), 2.76(br-t,4H), 3.58(br-t,4H), 7.35(d,J=8.4Hz,2H), 7.45(br-t,1H), 7.58(br-t,1H), 7.66(s,1H), 7.78(d,J=8.0Hz,1H), 8.07(d,J=8.4Hz,1H), 8.11(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/IPE, to give the title compound as a yellow powder.

Hydrochloride:

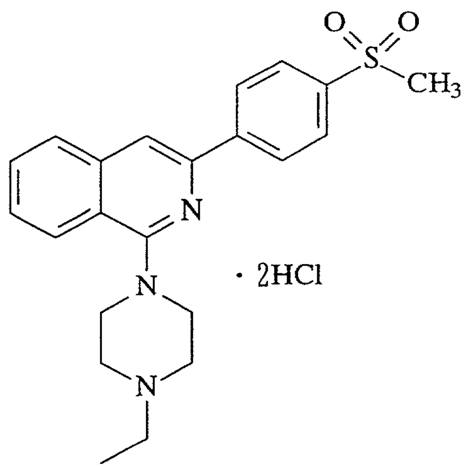
m.p.; 215-218°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.4Hz,3H), 2.54(s,3H), 3.19-3.26(m,2H), 3.31-3.38(m,2H), 3.54(br-t,2H), 3.62(br-d,2H), 3.99(br-d,2H), 7.39(d,J=8.6Hz,2H), 7.60(br-t,1H), 7.74(br-t,1H), 7.98(d,J=7.6Hz,1H), 8.08(s,1H),

8.11(d,J=8.4Hz,1H), 8.16(d,J=8.6Hz,2H), 11.14(br-s,1H).

MS(FAB) m/z 364$(M+H)^+$.

<u>Example 342</u> <u>Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(4-methylsulfonylphenyl)isoquinoline dihydrochloride</u>



· 2HCl

According to the method of Example 10-1, N-methyl-2-methylbenzamide (5.97 g) and 4-cyanothioanisole (5.97 g) were reacted, to give 3-(4-methylthiophenyl)isoquinolin-1-one (5.00 g).

The resulting 3-(4-methylthiophenyl)isoquinolin-1-one (2.18 g) was reacted with phosphorus oxychloride (20 ml) according to the method of Example 10-2, to give 1-chloro-3-(4-methoxythiophenyl)isoquinoline. N-Formylpiperazine (4.66 g), potassium carbonate (1.13 g) and dimethyl sulfoxide (20 ml) were added to the resulting product as it was, and the resulting mixture was reacted at 100°C overnight. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and purified water. The ethyl acetate layer was washed with water (six times) and brine, and dried over

magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (ethyl acetate/n-hexane system), to give 1-(4-formylpiperazin-1-yl)-3-(4-methylthiophenyl)isoquinoline (2.03 g) as a colorless amorphous.

The resulting 1-(4-formylpiperazin-1-yl)-3-(4-methylthiophenyl)isoquinoline (0.80 g) was dissolved in chloroform (40 ml), and the mixture was stirred under ice-cooling, to which was then added m-chloroperbenzoic acid (2.63 g) dissolved in chloroform (20 ml), and the mixture was stirred overnight. A 5N aqueous solution of sodium hydroxide was added to the resulting mixture, which was then extracted with chloroform. The organic layer was washed sequentially with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (ethyl acetate/n-hexane system), to give 1-(4-formylpiperazin-1-yl)-3-(4-methylsulfonylphenyl)isoquinoline (0.80 g).

To the resulting 1-(4-formylpiperazin-1-yl)-3-(4-methylsulfonylphenyl)isoquinoline (0.78 g) were added ethanol (30 ml) and a 8N aqueous solution of sodium hydroxide (740 ml), followed by heating under reflux in nitrogen atmosphere for 4 hr. The solvent was evaporated, and to the resulting residue were added water and ethyl acetate, and the organic layer was separated. Then, it was washed with brine, dried over magnesium sulfate. The solvent was evaporated, to give 1-(piperazin-

1-yl)-3-(4-methylsulfonylphenyl)isoquinoline (0.62 g) as a pale yellow amorphous.

The resulting 1-(piperazin-1-yl)-3-(4-methylsulfonylphenyl)isoquinoline (0.61 g) was dissolved in N,N-dimethylformamide (5 ml), followed by the addition of triethylamine (255 ml) and ethyl iodide (146 ml), and the mixture was sealed for overnight reaction at 50°C. Water was added to the reaction solution, and then it was extracted with ethyl acetate. The ethyl acetate layer was washed with water (three times) and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was recrystallized from ethyl acetate/n-hexane, to give 0.46 g of the free compound of the title compound as a pale brown powder.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.57(q,J=7.2Hz,2H), 2.77(br-t,4H), 3.10(s,3H), 3.60(br-t,4H), 7.54(br-t,1H), 7.64(br-t,1H), 7.78(s,1H), 7.84(d,J=8.0Hz,1H), 8.03(d,J=8.4Hz,2H), 8.11(d,J=8.4Hz,1H), 8.36(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/IPE, to give the title compound as a yellow powder.

Hydrochloride:

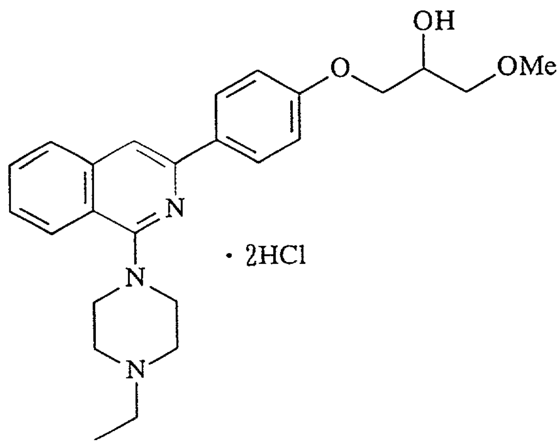
m.p.; 216.5-218°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 3.23(br-s,2H), 3.28(s,3H), 3.31-3.40(m,2H), 3.55(br-t,2H), 3.63(br-d,2H), 4.04(br-d,2H), 7.68(br-t,1H), 7.80(br-t,1H),

8.05(d,J=7.6Hz,1H), 8.06(d,J=8.4Hz,,2H), 8.16(d,J=8.4Hz,1H), 8.28(s,1H), 8.46(d,J=8.4Hz,2H), 11.02(br-s,1H).

MS(FAB) m/z 396(M+H)$^+$.

Example 343 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxy-3-methoxypropoxy)phenyl]isoquinoline dihydrochloride



According to the method of Example 7, 1-(4-ethylpiperazin-1-yl)-3-(4-hydroxyphenyl)isoquinoline was obtained.

To the resulting 1-(4-ethylpiperazin-1-yl)-3-(4-hydroxyphenyl)isoquinoline (0.52 g) were added dimethyl sulfoxide (5 ml), 2-(methoxymethyl)oxirane (3 ml) and potassium carbonate (0.21 g), and the resulting mixture was reacted in a sealed tube at 120°C for 1 day. Water was added to the reaction solution, and then it was extracted with ethyl acetate. The ethyl acetate layer was washed with water (six times) and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.15 g of

the free compound of the title compound as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.76(br-t,4H), 3.43(s,3H), 3.55-3.61(m,6H), 4.05-4.12(m,2H), 4.18-4.23(m,1H), 7.01(d,J=9.2Hz,2H), 7.43(br-t,1H), 7.56(br-t,1H), 7.61(s,1H), 7.76(d,J=8.0Hz,1H), 8.05(d,J=8.0Hz,1H), 8.11(d,J=8.8Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/IPE, to give the title compound as a yellow powder.

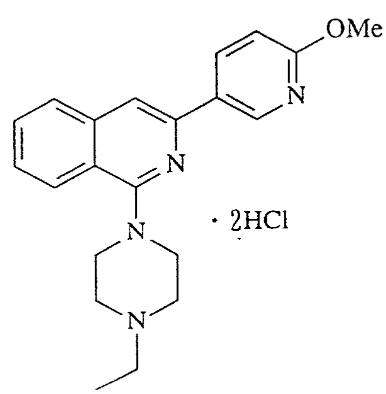
Hydrochloride:

m.p.; 216.5-218°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 3.20-3.26(m,2H), 3.30(s,3H), 3.33-3.55(m,6H), 3.62(br-d,2H), 3.94-4.04(m,5H), 7.07(d,J=9.0Hz,2H), 7.57(br-t,1H), 7.72(br-t,1H), 7.96(d,J=8.0Hz,1H), 8.00(s,1H), 8.10(d,J=8.8Hz,1H), 8.15(d,J=9.0Hz,2H), 10.99(br-s,1H).

MS(FAB) m/z 422(M+H)$^+$.

Example 344 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(2-methoxypyridin-5-yl)isoquinoline



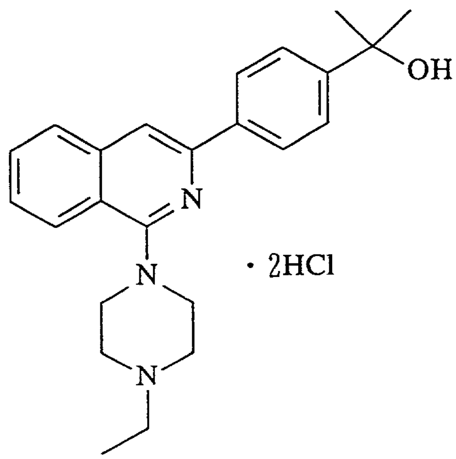
2-Methoxy-5-tributylstannylpyridine (1.41 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.57 g) obtained in Example 28-2 were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.10 g) in xylene in nitrogen atmosphere for 30 min. After cooling, the reaction solution was filtered and extracted in 2N hydrochloric acid. The aqueous layer was washed with ethyl acetate twice. The resulting aqueous layer was adjusted to pH 10 with a 8N aqueous solution of sodium hydroxide, and then extracted with ethyl acetate. The extract was washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.38 g of the free compound of the title compound as a pale brown powder.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 2.53(q,J=7.2Hz,2H), 2.72(br-t,4H), 3.57(br-t,4H), 4.00(s,3H), 6.82(d,J=8.8Hz,1H), 7.43(br-t,1H), 7.54(s,1H), 7.55(br-t,1H), 7.74(d,J=8.0Hz,1H), 8.04(d,J=8.4Hz,1H), 8.30(dd,J=2.4,8.8Hz,1H), 8.97(d,J=2.4Hz,1H).

MS(FAB) m/z 349$(M+H)^+$.

Example 345 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(1-hydroxy-1-methylethyl)phenyl]isoquinoline



4-(2-Methyl-1,3-dioxolan-2-yl)phenylboric acid (0.41 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.62 g) were reacted in the presence of tetrakistriphenylphosphinepalladium(0) (0.11 g) in toluene (50 ml) and a 10% aqueous solution of sodium carbonate (30 ml) in nitrogen atmosphere at 120°C for 30 min. The organic layer was separated, washed with brine and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 1-(4-ethylpiperazin-1-yl)-3-[4-(2-methyl-1,3-dioxolan-2-yl)phenyl]isoquinoline.

The resulting compound was dissolved in ethyl acetate and extracted with 2N hydrochloric acid. The aqueous layer was washed with ethyl acetate, adjusted to pH 10 with a 8N aqueous solution of sodium hydroxide, and then extracted with ethyl acetate. The extract was washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, to give 0.55 g of 1-(4-

ethylpiperazin-1-yl)-3-(4-acetylphenyl)isoquinoline as a pale brown viscous oil.

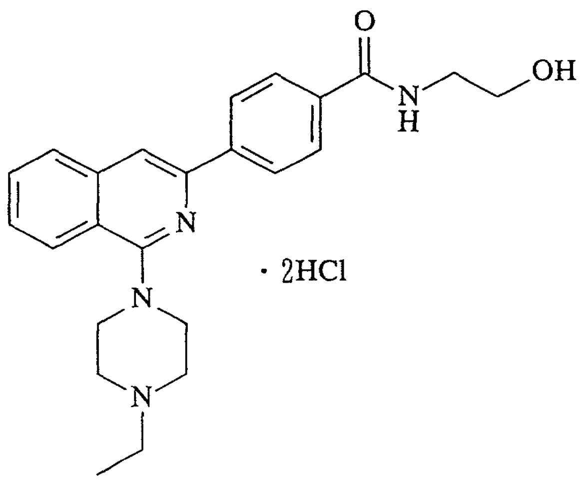
The resulting 1-(4-ethylpiperazin-1-yl)-3-(4-acetylphenyl)isoquinoline (0.10 g) was dissolved in tetrahydrofuran (10 ml) and stirred under ice-cooling, to which was then added 3.0M methylmagnesium bromide/ether solution (1.1 ml), and the mixture was further stirred for 1.5 hr. An aqueous solution of saturated ammonium chloride, a 10% aqueous solution of sodium carbonate and ethyl acetate were added to the resulting mixture, the mixture was stirred. The organic layer was separated, and then it was washed with brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.05 g of the free compound of the title compound as a pale brown amorphous.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 1.63(s,6H), 2.56(q,J=7.2Hz,2H), 2.76(br-t,4H), 3.59(br-t,4H), 7.45(br-t,1H), 7.56-7.61(m,3H), 7.68(s,1H), 7.78(d,J=8.0Hz,1H), 8.07(d,J=7.6Hz,1H), 8.14(d,J=8.4Hz,2H).

MS(FAB) m/z 376(M+H)$^+$.

Example 346 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-{4-[N-(2-hydroxyethyl)carbamoyl]phenyl}isoquinoline dihydrochloride



N-(2-Benzyloxyethyl)-4-tributylstannylbenzamide (1.23 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.49 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.13 g) in xylene in nitrogen atmosphere for 3 hr. After cooling, the reaction solution was filtered and concentrated. The resulting residue was purified by silica gel column chromatography (chloroform/methanol system). The resulting product was dissolved in ethyl acetate and extracted with 2N hydrochloric acid. The aqueous layer was washed with ethyl acetate, adjusted to pH 10 with a 8N aqueous solution of sodium hydroxide, and then extracted with ethyl acetate. The extract was washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, to give 1-(4-ethylpiperazin-1-yl)-3-{4-[N-(2-benzyloxyethyl)carbamoyl]phenyl}isoquinoline (0.17 g) as a pale brown viscous oil.

The resulting 1-(4-ethylpiperazin-1-yl)-3-{4-[N-(2-

benzyloxyethyl)carbamoyl]phenyl}isoquinoline (0.17 g) was converted into a hydrochloride in a conventional manner. The resulting hydrochloride was dissolved in methanol (10 ml), followed by the addition of 10% palladium/carbon catalyst (0.03 g), and the catalytic reduction was conducted at atmospheric pressure for 2 days. The catalyst was filtered off, and the solvent was evaporated. Water was added to the resulting residue, to which was then added sodium carbonate to adjust the resulting solution to pH 8, and the resulting mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.05 g of the free compound of the title compound as a pale brown amorphous.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.76(br-t,4H), 2.84(br-s,1H), 3.58(br-t,4H), 3.65(br-q,2H), 3.85(t,J=5.0Hz,2H), 6.88(t,J=5.6Hz,1H), 7.48(br-t,1H), 7.58(br-t,1H), 7.69(s,1H), 7.75(d,J=7.6Hz,1H), 7.87(d,J=8.4Hz,2H), 8.06(d,J=8.0Hz,1H), 8.19(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/IPE, to give the title compound as a yellow powder.

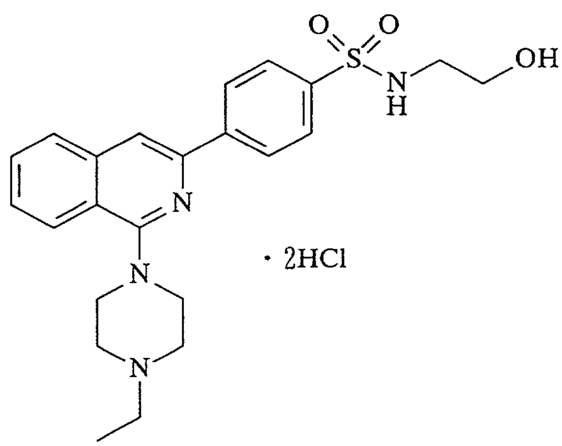
Hydrochloride:

m.p.; 154-155°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 3.20-3.27(m,2H), 3.32-3.40(m,4H), 3.51-3.57(m,4H), 3.64(br-d,2H), 4.02(br-d,2H), 7.65(br-t,1H), 7.78(br-t,1H), 8.00-8.03(m,3H), 8.14(d,J=8.4Hz,1H), 8.22(s,1H), 8.29(d,J=8.4Hz,2H), 8.58(t,J=5.6Hz,1H), 10.96(br-s,1H).

MS(FAB) m/z 405(M+H)$^+$.

Example 347 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-{4-[N-(2-hydroxyethyl)sulfamoyl]phenyl}isoquinoline dihydrochloride



N-(2-Benzyloxyethyl)4-tributylstannylbenzenesulfonamide (0.92 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.42 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.09 g) in xylene in nitrogen atmosphere for 45 min. After cooling, the reaction solution was filtered and concentrated. The residue was purified by silica gel column chromatography (chloroform/methanol system). The resulting product was dissolved in ethyl acetate and extracted with 2N hydrochloric

acid. The aqueous layer was washed with ethyl acetate, adjusted to pH 10 with a 8N aqueous solution of sodium hydroxide, and then extracted with ethyl acetate. The extract was washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, to give 1-(4-ethylpiperazin-1-yl)-3-{4-[N-(2-benzyloxyethyl)sulfamoyl]phenyl}isoquinoline (0.34 g) as a pale brown oil.

The resulting 1-(4-ethylpiperazin-1-yl)-3-{4-[N-(2-benzyloxyethyl)sulfamoyl]phenyl}isoquinoline (0.34 g) was converted into a hydrochloride in a conventional manner. The resulting hydrochloride was dissolved in methanol (20 ml), followed by the addition of 10% palladium/carbon catalyst (0.08 g), and the catalytic reduction was conducted at atmospheric pressure for 2 days. The catalyst was filtered off, and the solvent was evaporated. Water was added to the resulting residue, to which was then added sodium carbonate to adjust the resulting solution to pH 8, and the resulting mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), give 0.19 g of the free compound of the title compound as a pale brown amorphous.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.57(q,J=7.2Hz,2H), 2.77(br-t,4H), 3.16(br-q,2H), 3.60(br-

t,2H), 3.72(t,J=5.0Hz,2H), 4.93(t,J=5.8Hz,1H), 7.53(br-t,1H), 7.64(br-t,1H), 7.76(s,1H), 7.82(d,J=8.8Hz,1H), 7.96(d,J=8.4Hz,2H), 8.10(d,J=7.6Hz,1H), 8.32(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/IPE, to give the title compound as a yellow powder.

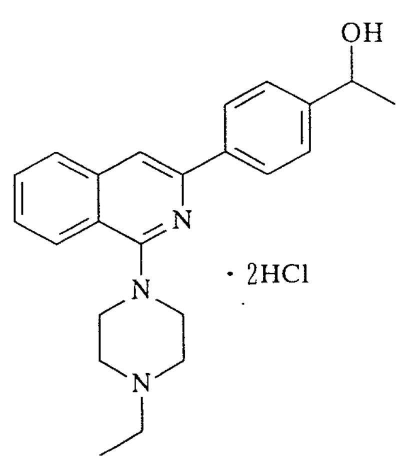
Hydrochloride:

m.p.; 136-138.5°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 2.84(br-q,2H), 3.21-3.28(m,2H), 3.34-3.41(m,2H), 3.39(t,J=6.4Hz,2H), 3.51(br-t,2H), 3.63(br-d,2H0,4.04(br-d,2H), 7.67(br-t,1H), 7.71(br-t,1H), 7.79(br-t,1H), 7.93(d,J=8.6Hz,2H), 8.04(d,J=8.0Hz,1H), 8.16(d,J=8.4Hz,1H), 8.24(s,1H), 8.40(d,J=8.6Hz,2H), 10.69(br-s,1H).

MS(FAB) m/z 441(M+H)$^+$.

Example 348 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(1-hydroxyethyl)phenyl]isoquinoline dihydrochloride or compound identified by the following analytical data and synthetic procedures



1-(4-Ethylpiperazin-1-yl)-3-(4-acetylphenyl)isoquinoline (0.20 g) obtained as an intermediate in Example 345 was dissolved in methanol (20 ml), followed by the addition of sodium borohydride until the starting material disappeared on TLC. The solvent was evaporated, and to the resulting residue were added water and a 8N aqueous solution of sodium hydroxide to adjust the resulting solution to pH 10, which was then extracted with ethyl acetate. Then, the extract was washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.13 g of the free compound of the title compound as a pale brown amorphous.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 1.54(d,J=6.4Hz,3H), 2.43(br-s,1H), 2.55(q,J=7.2Hz,2H), 2.74(br-t,4H), 3.57(br-t,4H), 4.95(q,J=6.4Hz,1H), 7.45(br-t,1H), 7.47(d,J=8.4Hz,2H), 7.58(br-t,1H), 7.67(s,1H), 7.77(d,J=8.0Hz,1H), 8.06(d,J=8.4Hz,1H), 8.14(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/IPE, to give the title compound as a yellow powder.

Hydrochloride:

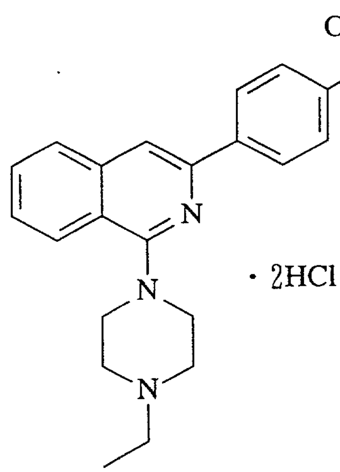
m.p.; 135.5-136°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H),

1.37(d,J=6.4Hz,3H), 3.20-3.27(m,2H), 3.32-3.39(m,2H), 3.51(br-t,2H), 3.63(br-d,2H), 4.01(br-d,2H), 4.79(q,J=6.4Hz,1H), 7.47(d,J=8.4Hz,2H), 7.61(br-t,1H), 7.74(br-t,1H), 7.99(d,J=8.4Hz,1H), 8.07(s,1H), 8.12(d,J=8.0Hz,1H), 8.15(d,J=8.4Hz,2H), 10.79(br-s,1H).

MS(FAB) m/z 362$(M+H)^+$.

Example 349 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(propylsulfonyl)phenyl]isoquinoline dihydrochloride



(4-Tributylstannylphenyl)propylsulfone (1.24 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.54 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.15 g) in xylene in nitrogen atmosphere for 1 day. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid, and the resulting aqueous layer was washed with ethyl acetate, adjusted to pH 10 with a 8N aqueous solution of sodium hydroxide, which was then extracted with ethyl acetate. The extract was washed

with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.60 g of the free compound of the title compound as a pale brown amorphous.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.01(t,J=7.2Hz,3H), 1.18(t,J=7.2Hz,3H), 1.77-1.83(m,2H), 2.56(q,J=7.2Hz,2H), 2.77(br-t,4H), 3.09-3.13(m,2H), 3.59(br-t,4H), 7.54(br-t,1H), 7.62(br-t,1H), 7.83(br-d,1H), 7.98(d,J=8.8Hz,2H), 8.10(br-d,1H), 8.35(d,J=8.8Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/IPE, to give the title compound as a yellow powder.

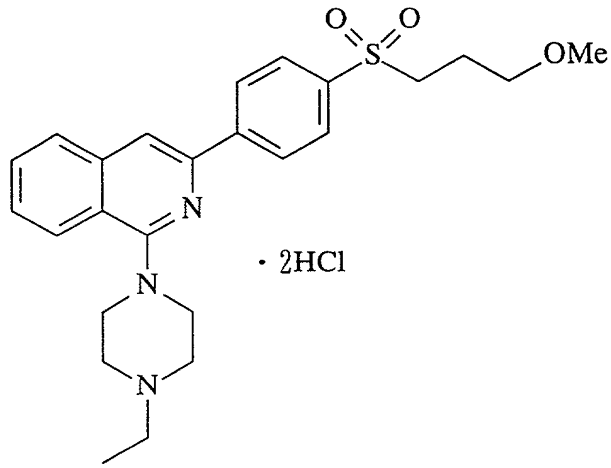
Hydrochloride:

m.p.; 240.5-242°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.94(t,J=7.4Hz,3H), 1.34(t,J=7.2Hz,3H), 1.55-1.65(m,2H), 3.20-3.27(m,2H), 3.28-3.40(m,4H), 3.50-3.64(m,4H), 4.03(br-d,2H), 7.68(br-t,1H), 7.80(br-t,1H), 8.02(d,J=8.4Hz,2H), 8.05(d,J=7.6Hz,1H), 8.16(d,J=8.4Hz,1H), 8.28(s,1H), 8.47(d,J=8.4Hz,2H), 11.25(br-s,1H).

MS(FAB) m/z 424$(M+H)^+$.

Example 350 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-{4-[(3-methoxypropyl)sulfonyl]phenyl}isoquinoline



(4-Tributylstannylphenyl)(3-methoxypropyl)sulfone (1.70 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.93 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.20 g) in xylene in nitrogen atmosphere for 1 day. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid, and the resulting aqueous layer was washed with ethyl acetate and adjusted to pH 10 with a 8N aqueous solution of sodium hydroxide, which was then extracted with ethyl acetate, washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.87 g of the free compound of the title compound as a pale brown amorphous.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.99-

2.06(m,2H), 2.57(q,J=7.2Hz,2H), 2.77(br-t,4H), 3.22-3.26(m,2H), 3.28(s,3H), 3.44(t,J=6.2Hz,2H), 3.61(br-t,4H), 7.53(br-t,1H), 7.64(br-t,1H), 7.78(s,1H), 7.84(d,J=8.0Hz,1H), 7.99(d,J=8.6Hz,2H), 8.11(d,J=8.4Hz,1H), 8.35(d,J=8.6Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/ether, to give the title compound as a yellow powder.

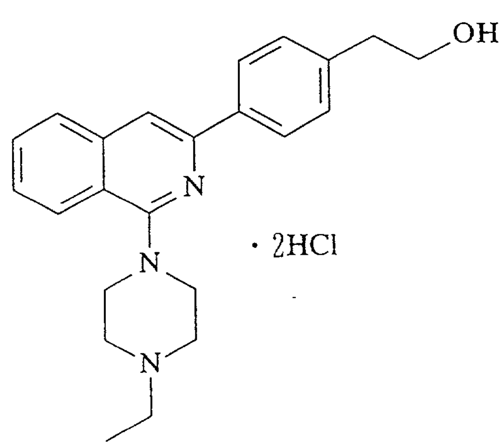
Hydrochloride:

m.p.; 177.5-180°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 1.76-1.83(m,2H), 3.18(s,3H), 3.21-3.28(m,2H), 3.33-3.39(m,6H), 3.53(br-t,2H), 3.64(br-d,2H), 4.04(br-d,2H), 7.68(br-t,1H), 7.80(br-t,1H), 8.03(d,J=8.8Hz,2H), 8.05(d,J=8.0Hz,1H), 8.17(d,J=8.0Hz,1H), 8.29(s,1H), 8.47(d,J=8.8Hz,2H), 10.85(br-s,1H).

MS(FAB) m/z 454(M+H)$^+$.

Example 351 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxyethyl)phenyl]isoquinoline dihydrochloride



4-(2-Benzyloxyethyl)phenylboric acid (0.40 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.65 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.09 g) in toluene (50 ml) and a 10% aqueous solution of sodium carbonate (30 ml) in nitrogen atmosphere for 1 hr. To the mixture was additionally added 4-(2-benzyloxyethyl)phenylboric acid (0.40 g), and the mixture was heated under reflux for 1.5 hr. 4-(2-Benzyloxyethyl)phenylboric acid (0.40 g) was again added, and the mixture was heated under reflux overnight. The organic layer was separated, and it was extracted with 2N hydrochloric acid twice. The resulting aqueous layer was washed with ethyl acetate, adjusted to pH 10 with a 8N aqueous solution of sodium hydroxide, extracted with ethyl acetate, washed with a 10% aqueous solution of sodium carbonate and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system, and then ethyl acetate/acetone system), to give 1-(4-ethylpiperazin-1-yl)-3-[4-(2-benzyloxyethyl)phenyl]isoquinoline (0.48 g) as a colorless viscous oil.

The resulting 1-(4-ethylpiperazin-1-yl)-3-[4-(2-benzyloxyethyl)phenyl]isoquinoline (0.46 g) was converted into a hydrochloride in a conventional manner. The resulting hydrochloride was then dissolved in methanol (50 ml), followed by the addition of 10% palladium/carbon catalyst (0.10 g), and

the catalytic reduction was conducted at atmospheric pressure overnight. The catalyst was filtered off, while the solvent was evaporated. Water was added thereto, followed by the addition of a 1N aqueous solution of sodium hydroxide to adjust to pH 8, and then the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and evaporated. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.24 g of the free compound of the title compound as a pale brown viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.76(br-t,4H), 2.94(t,J=6.6Hz,2H), 3.59(br-t,4H), 3.91(t,J=6.6Hz,2H), 7.34(d,J=8.4Hz,2H), 7.46(br-t,1H), 7.59(br-t,1H), 7.68(s,1H), 7.79(d,J=8.0Hz,1H), 8.08(d,J=8.4Hz,1H), 8.12(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/ether, to give the title compound as a yellow powder.

Hydrochloride:

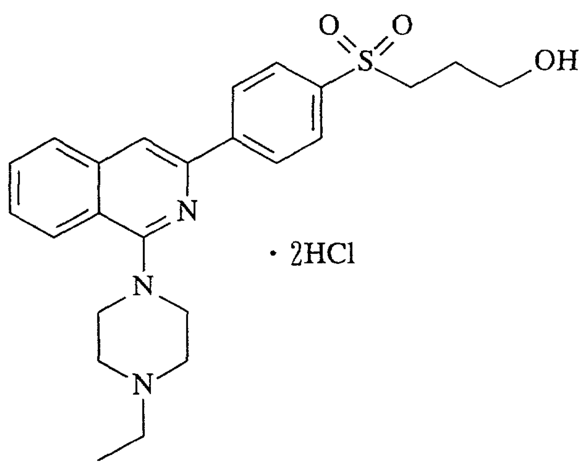
m.p.; 134-136°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 2.79(t,J=7.0Hz,2H), 3.19-3.26(m,2H), 3.30-3.38(m,2H), 3.55(br-t,2H), 3.62(br-d,2H), 3.65(t,J=7.0Hz,2H), 3.99(br-d,2H), 7.36(d,J=8.4Hz,2H), 7.60(br-t,1H), 7.74(br-t,1H),

7.98(d,J=8.0Hz,1H), 8.05(s,1H), 8.11(d,J=8.4Hz,2H), 8.11(d,J=8.4Hz,1H), 11.12(br-s,1H).

MS(FAB) m/z 362(M+H)$^+$.

Example 352 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxypropyl)sulfonylphenyl]isoquinoline dihydrochloride



(4-Tributylstannylphenyl)(3-benzyloxypropyl)sulfone (5.78 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (2.13 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.58 g) in xylene in nitrogen atmosphere for 7 hr. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid, and the resulting aqueous layer was washed with ethyl acetate and adjusted to pH 10 with a 8N aqueous solution of sodium hydroxide, which was then extracted with ethyl acetate. The extract was washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column

chromatography (chloroform/methanol system), to give 1-(4-ethylpiperazin-1-yl)-3-[4-(3-benzyloxypropyl)sulfonylphenyl]isoquinoline (2.56 g) as a pale brown amorphous.

The resulting 1-(4-ethylpiperazin-1-yl)-3-[4-(2-benzyloxyethyl)sulfonylphenyl]isoquinoline (2.56 g) was converted into a hydrochloride in a conventional manner. The resulting hydrochloride was then dissolved in methanol (50 ml), followed by the addition of 10% palladium/carbon catalyst (0.07 g), and the catalytic reduction was conducted at atmospheric pressure overnight. The 10% palladium/carbon catalyst (0.05 g) was additionally added thereto, and the catalytic reduction was conducted at atmospheric pressure for 1 day. The catalyst was filtered off, while the solvent was evaporated. Water was added to the resulting residue, followed by the addition of a 1N aqueous solution of sodium hydroxide to adjust to pH 8, and the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 1.23 g of the free compound of the title compound as a pale yellow amorphous.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.98-2.05(m,2H), 2.56(q,J=7.2Hz,2H), 2.76(br-t,4H), 3.27-3.31(m,2H), 3.59(br-t,4H), 3.75(t,J=6.0Hz,2H), 7.53(br-t,1H),

7.64(br-t,1H), 7.77(s,1H), 7.83(d,J=7.6Hz,1H), 7.99(d,J=8.4Hz,2H), 8.09(d,J=8.4Hz,1H), 8.34(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/ether, to give the title compound as yellow needles.

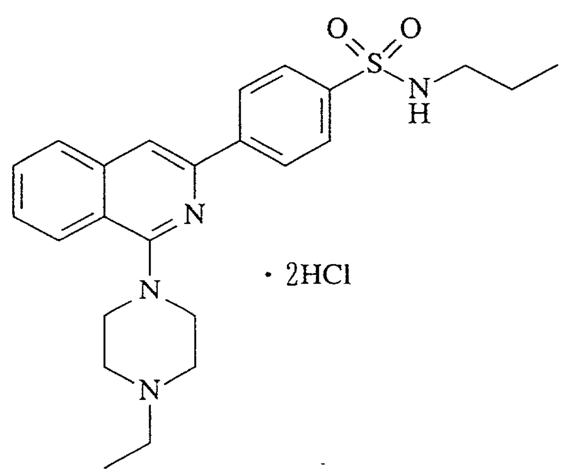
Hydrochloride:

m.p.; 213-215°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 1.67-1.74(m,2H), 3.22-3.28(m,2H), 3.33-3.44(m,6H), 3.51(br-t,2H), 3.64(br-d,2H), 4.05(br-d,2H), 7.68(br-t,1H), 7.80(br-t,1H), 8.02(d,J=8.4Hz,2H), 8.05(d,J=8.0Hz,1H), 8.17(d,J=8.8Hz,1H), 8.29(s,1H), 8.47(d,J=8.4Hz,2H), 10.68(br-s,1H).

MS(FAB) m/z 439(M+H)$^+$.

<u>Example 353 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(N-propylsulfamoyl)phenyl]isoquinoline dihydrochloride</u>



N-Propyl-4-tributylstannylbenzenesulfonamide (1.05 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.46 g)

were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.12 g) in xylene in nitrogen atmosphere overnight. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid, and the resulting aqueous layer was washed with ethyl acetate, adjusted to pH 10 with a 8N aqueous solution of sodium hydroxide, and then extracted with ethyl acetate. The extract was washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.41 g of the free compound of the title compound as a pale brown amorphous.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.89(t,J=7.2Hz,3H), 1.18(t,J=7.2Hz,3H), 1.52(tq,J=7.2,7.2Hz,2H), 2.57(q,J=7.2Hz,2H), 2.77(br-t,4H), 2.97(q,J=7.2Hz,2H), 3.60(br-t,4H), 4.38(br-t,1H), 7.52(br-t,1H), 7.63(br-t,1H), 7.77(s,1H), 7.83(d,J=8.4Hz,1H), 7.95(d,J=8.4Hz,2H), 8.10(d,J=8.4Hz,1H), 8.31(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a pale brown powder.

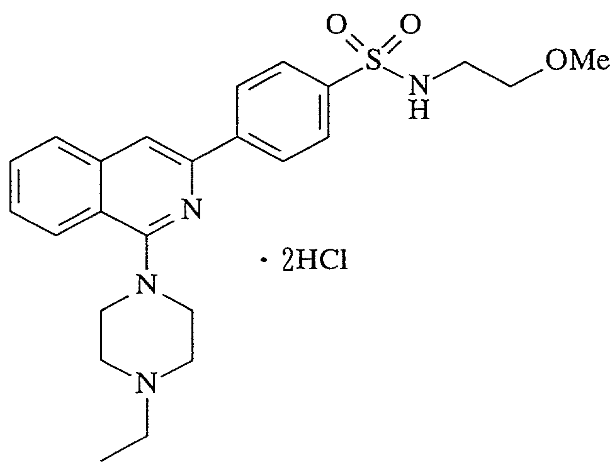
Hydrochloride:

m.p.; 226.5-227.5°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.81(t,J=7.2Hz,3H), 1.33(t,J=7.2Hz,3H), 1.40(tq,J=7.2Hz,2H), 2.74(br-q,2H), 3.22-3.28(m,2H), 3.32-3.41(m,2H), 3.50(br-t,2H), 3.64(br-d,2H), 4.05(br-d,2H), 7.65-4.70(m,2H), 7.79(br-t,1H), 7.91(d,J=8.8Hz,2H), 8.03(d,J=8.0Hz,1H), 8.16(d,J=8.4Hz,1H), 8.24(s,1H), 8.40(d,J=8.8Hz,2H), 10.56(br-s,1H).

MS(FAB) m/z 439(M+H)$^+$.

Example 354 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-{4-[N-(2-methoxyethyl)sulfamoyl]phenyl}isoquinoline dihydrochloride



N-(2-Methoxyethyl)-4-tributylstannylbenzenesulfonamide (1.07 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.45 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.12 g) in xylene in nitrogen atmosphere overnight. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The

filtrate was extracted with 2N hydrochloric acid, and the resulting aqueous layer was washed with ethyl acetate, adjusted to pH 10 with a 8N aqueous solution of sodium hydroxide, and then extracted with ethyl acetate. The extract was washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.43 g of the free compound of the title compound as a pale brown amorphous.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.57(q,J=7.2Hz,2H), 2.77(br-t,4H), 3.17(dt,J=5.0,6.0Hz,2H), 3.28(s,3H), 3.43(t,J=5.0Hz,2H), 3.60(br-t,4H), 4.87(t,J=6.0Hz,1H), 7.52(br-t,1H), 7.63(br-t,1H), 7.77(s,1H), 7.84(d,J=8.0Hz,1H), 7.95(d,J=8.4Hz,2H), 8.10(d,J=9.2Hz,1H), 8.31(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a pale brown powder.

Hydrochloride:

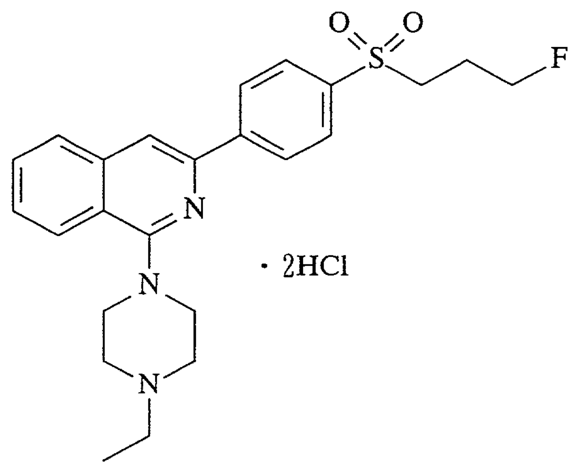
m.p.; 222-224°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 2.95(dt,J=5.8Hz,2H), 3.18(s,3H), 3.20-3.27(m,2H), 3.33(t,J=5.8Hz,2H), 3.36(br-t,2H), 3.56(br-t,2H), 3.63(br-

d,2H), 4.04(br-d,2H), 7.67(br-t,1H), 7.79(br-t,1H), 7.84(t,J=5.8Hz,1H), 7.93(d,J=8.4Hz,2H), 8.03(d,J=7.6Hz,1H), 8.16(d,J=8.0Hz,1H), 8.24(s,1H), 8.40(d,J=8.4Hz,2H), 11.09(br-s,1H).

MS(FAB) m/z 455$(M+H)^+$.

Example 355 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(3-fluoropropyl)sulfonylphenyl]isoquinoline dihydrochloride



Diethylaminosulfur trifluoride (DAST, 0.14 ml) was added to anhydrous methylene chloride (3 ml), and the resulting mixture was stirred at -78°C in nitrogen atmosphere, to which was then added a solution of 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxypropyl)sulfonylphenyl]isoquinoline (0.31 g) obtained in Example 352 in methylene chloride (5 ml), and the mixture was further stirred for 6 hr. DAST (0.09 ml) was further added thereto, and the resulting mixture was further stirred overnight. The bulk temperature was raised to room temperature. The reaction solution was diluted with chloroform, followed by the addition of a 10% aqueous solution of sodium carbonate. The

organic layer was separated, and then it was washed with brine and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.23 g of the free compound of the title compound as a pale brown viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.11-2.26(m,2H), 2.56(q,J=7.2Hz,2H), 2.77(br-t,4H), 3.26-3.30(m,2H), 3.60(br-t,4H), 4.53(dt,J=5.6,46.8Hz,2H), 7.53(br-t,1H), 7.64(br-t,1H), 7.77(s,1H), 7.83(d,J=8.0Hz,1H), 7.99(d,J=8.4Hz,2H), 8.10(d,J=8.4Hz,1H), 8.36(d,J=8.8Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/ether, to give the title compound as pale yellow needles.

Hydrochloride:

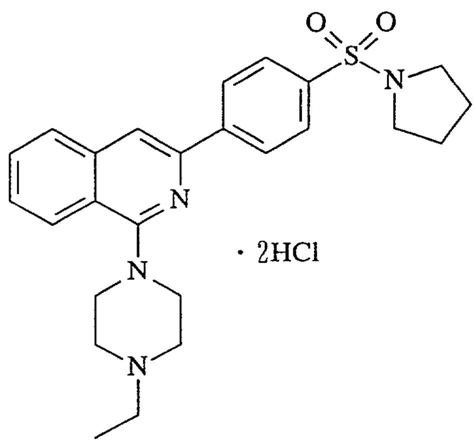
m.p.; 224-225°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 1.90-2.04(m,2H), 3.22-3.28(m,2H), 3.32-3.41(m,2H), 3.44-3.54(m,4H), 3.64(br-d,2H), 4.05(br-d,2H), 4.50(dt,J=6.0,46.8Hz,2H), 7.69(br-t,1H), 7.81(br-t,1H), 8.03-8.06(m,3H), 8.17(d,J=8.4Hz,1H), 8.30(s,1H), 8.48(d,J=8.4Hz,2H), 10.62(br-s,1H).

MS(FAB) m/z 442$(M+H)^+$.

Example 356 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-

(pyrrolidin-1-yl)sulfonylphenyl]isoquinoline dihydrochloride



Pyrrolidine 4-tributylstannylbenzenesulfonamide (1.17 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.64 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.09 g) in xylene in nitrogen atmosphere overnight. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid. The aqueous layer was washed with ethyl acetate. Then, it was adjusted to pH 10 by a 8N aqueous solution of sodium hydroxide, extracted with ethyl acetate, washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (toluene/acetone system), to give 0.47 g of the free compound of the title compound as a pale brown amorphous.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.76-

1.79(m,4H), 2.57(q,J=7.2Hz,2H), 2.77(br-t,4H), 3.28-3.31(m,2H), 3.60(br-t,4H), 7.52(br-t,1H), 7.64(br-t,1H), 7.77(s,1H), 7.83(d,J=8.0Hz,1H), 7.92(d,J=8.6Hz,2H), 8.10(d,J=8.4Hz,1H), 8.32(d,J=8.6Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a pale brown powder.

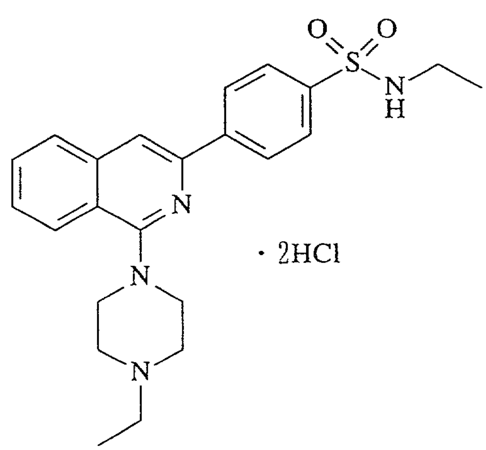
Hydrochloride:

m.p.; 238.5-240°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 1.65-1.68(m,4H), 3.18-3.27(m,6H), 3.32-3.40(m,2H), 3.56(br-t,2H), 3.63(br-d,2H), 4.02(br-d,2H), 7.68(br-t,1H), 7.80(br-t,1H), 7.94(d,J=8.8Hz,2H), 8.05(d,J=7.6Hz,1H), 8.16(d,J=8.8Hz,1H), 8.27(s,1H), 8.45(d,J=8.4Hz,2H), 11.17(br-s,1H).

MS(FAB) m/z 451$(M+H)^+$.

Example 357 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(N-ethylsulfamoyl)phenyl]isoquinoline dihydrochloride



N-Ethyl-4-tributylstannylbenzenesulfonamide (1.05 g)

and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.61 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.09 g) in xylene in nitrogen atmosphere overnight. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid, and the resulting aqueous layer was washed with ethyl acetate. Then, it was adjusted to pH 10 by a 8N aqueous solution of sodium hydroxide, extracted with ethyl acetate, washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give the free compound of the title compound (0.49 g) as a pale brown amorphous.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.14(t,J=7.2Hz,3H), 1.18(t,J=7.2Hz,3H), 2.57(q,J=7.2Hz,2H), 2.77(br-t,4H), 3.07(dq,J=6.0,7.2Hz,2H), 3.60(br-t,4H), 4.30(t,J=6.0Hz,1H), 7.52(br-t,1H), 7.63(br-t,1H), 7.77(s,1H), 7.83(d,J=8.8Hz,1H), 7.95(d,J=8.4Hz,2H), 8.10(d,J=8.4Hz,1H), 8.31(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a pale brown powder.

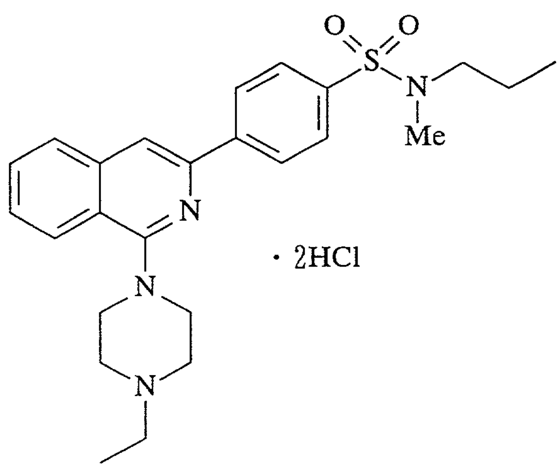
Hydrochloride:

m.p.; 147-149°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.00(t,J=7.2Hz,3H), 1.33(t,J=7.2Hz,3H), 2.79-2.86(m,2H), 3.21-3.27(m,2H), 3.32-3.4(m,2H), 3.53(br-t,2H), 3.63(br-d,2H), 4.04(br-d,2H), 7.64-7.69(m,2H), 7.79(br-t,1H), 7.92(d,J=8.4Hz,2H), 8.03(d,J=7.6Hz,1H), 8.16(d,J=8.4Hz,1H), 8.24(s,1H), 8.41(d,J=8.4Hz,2H), 10.86(br-s,1H).

MS(FAB) m/z 425(M+H)$^+$.

Example 358 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(N-methyl-N-propylsulfamoyl)phenyl]isoquinoline dihydrochloride



N-Methyl-N-propyl-4-tributylstannylbenzenesulfonamide (2.00 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.64 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.15 g) in xylene in nitrogen atmosphere overnight. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid, and the

resulting aqueous layer was washed with ethyl acetate. Then, it was adjusted to pH 10 by a 8N aqueous solution of sodium hydroxide, extracted with ethyl acetate, washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.56 g of the free compound of the title compound as a pale brown amorphous.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.95(t,J=7.2Hz,3H), 1.18(t,J=7.2Hz,3H), 1.59(tq,J=7.2,7.2Hz,2H), 2.57(q,J=7.2Hz,2H), 2.75-2.78(77H), 3.01(t,J=7.2Hz,2H), 3.60(br-t,4H), 7.52(br-t,1H), 7.63(br-t,1H), 7.77(s,1H), 7.83(d,J=8.0Hz,1H), 7.87(d,J=8.6Hz,2H), 8.10(d,J=8.0Hz,1H), 8.18(d,J=8.6Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a pale brown powder.

Hydrochloride:

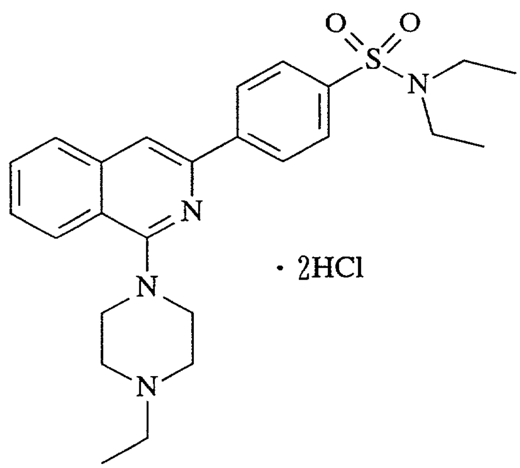
m.p.; 199.5-200.5°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.86(t,J=7.2Hz,3H), 1.34(t,J=7.2Hz,3H), 1.50(tq,J=7.2,7.2Hz,2H), 2.70(s,3H), 2.95(t,J=7.2Hz,2H), 3.20-3.27(m,2H), 3.32-3.40(m,2H), 3.56(br-t,2H), 3.63(br-d,2H), 4.02(br-d,2H), 7.68(br-t,1H),

7.80(br-t,1H), 7.90(d,J=8.8Hz,2H), 8.05(d,J=7.6Hz,1H), 8.16(d,J=8.4Hz,1H), 8.26(s,1H), 8.44(d,J=8.4Hz,2H), 11.18(br-s,1H).

MS(FAB) m/z 453$(M+H)^+$.

Example 359 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(N,N-diethylsulfamoyl)phenyl]isoquinoline dihydrochloride



N,N-Diethyl-4-tributylstannylbenzenesulfonamide (1.29 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.55 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.10 g) in xylene in nitrogen atmosphere overnight. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid, and the resulting aqueous layer was washed with ethyl acetate. Then, it was adjusted to pH 10 by a 8N aqueous solution of sodium hydroxide, extracted with ethyl acetate, washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the

resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.48 g of the free compound of the title compound as a pale brown amorphous.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,6H), 1.18(t,J=7.2Hz,3H), 2.57(q,J=7.2Hz,2H), 2.77(br-t,4H), 3.28(q,J=7.2Hz,4H), 3.60(br-t,4H), 7.52(br-t,1H), 7.63(br-t,1H), 7.76(s,1H), 7.83(d,J=8.8Hz,1H), 7.90(d,J=8.4Hz,2H), 8.10(d,J=8.4Hz,1H), 8.29(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a pale brown powder.

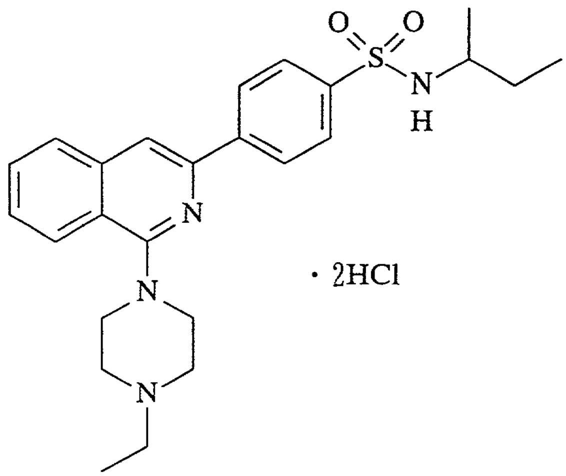
Hydrochloride:

m.p.; 210-212°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.07(t,J=7.2Hz,6H), 1.34(t,J=7.2Hz,3H), 3.18-3.26(m,6H), 3.32-3.39(m,2H), 3.56(br-t,2H), 3.62(br-d,2H), 4.02(br-d,2H), 7.67(br-t,1H), 7.79(br-t,1H), 7.92(d,J=8.8Hz,2H), 8.04(d,J=8.0Hz,1H), 8.16(d,J=8.4Hz,1H), 8.25(s,1H), 8.41(d,J=8.8Hz,2H), 11.22(br-s,1H).

MS(FAB) m/z 453$(M+H)^+$.

<u>Example 360 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-{4-[N-(1-methylpropyl)sulfamoyl]phenyl}isoquinoline dihydrochloride</u>



N-(1-Methylpropyl)-4-tributylstannylbenzenesulfonamide (0.98 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.42 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.08 g) in xylene in nitrogen atmosphere overnight. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid, and the resulting aqueous layer was washed with ethyl acetate. Then, it was adjusted to pH 10 by a 8N aqueous solution of sodium hydroxide, extracted with ethyl acetate, washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.36 g of the free compound of the title compound as a pale brown amorphous.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.83(t,J=7.2Hz,3H), 1.06(d,J=6.4Hz,3H), 1.17(t,J=7.2Hz,3H), 1.39-1.47(m,2H), 2.56(q,J=7.2Hz,2H), 2.76(br-t,4H), 3.28-3.34(m,1H), 3.59(br-t,4H), 4.75(d,J=8.0Hz,1H), 7.51(br-t,1H), 7.61(br-t,1H), 7.76(s,1H), 7.80(d,J=8.0Hz,1H), 7.98(d,J=8.8Hz,2H), 8.09(d,J=8.0Hz,1H), 8.31(d,J=8.8Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a pale brown powder.

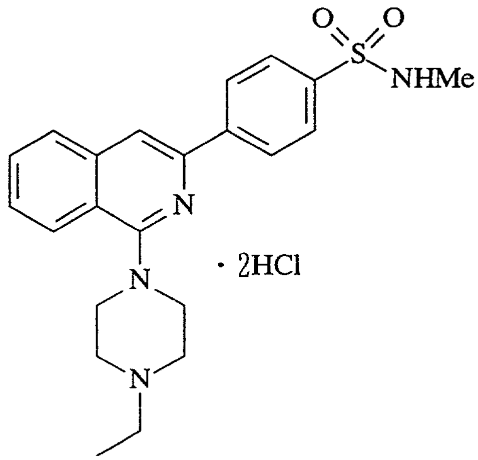
Hydrochloride:

m.p.; 155-156°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.74(t,J=7.2Hz,3H), 0.90(d,J=6.4Hz,3H), 1.30-1.37(m,5H), 3.08-3.27(m,3H), 3.33-3.40(m,2H), 3.54(br-t,2H), 3.63(br-d,2H), 4.04(br-d,2H), 7.62(d,J=7.6Hz,1H), 7.67(br-t,1H), 7.79(br-t,1H), 7.93(d,J=8.4Hz,2H), 8.03(d,J=8.4Hz,1H), 8.15(d,J=8.0Hz,1H), 8.25(s,1H), 8.40(d,J=8.4Hz,2H), 10.95(br-s,1H).

MS(FAB) m/z 453$(M+H)^+$.

Example 361 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(N-methylsulfamoyl)phenyl]isoquinoline dihydrochloride



· 2HCl

N-Methyl-4-tributylstannylbenzenesulfonamide (1.23 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.73 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.10 g) in xylene in nitrogen atmosphere overnight. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid, and the resulting aqueous layer was washed with ethyl acetate. Then, it was adjusted to pH 10 by a 8N aqueous solution of sodium hydroxide, extracted with ethyl acetate, washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the reuslting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.38 g of the free compound of the title compound as a pale brown amorphous.

Free compound:

^{1}H-NMR(400MHz, $CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H),

2.57(q,J=7.2Hz,2H), 2.71(s,1.5H), 2.72(s,1.5H), 2.77(br-t,4H), 3.60(br-t,4H), 4.35(br-q,1H), 7.53(br-t,1H), 7.64(br-t,1H), 7.77(s,1H), 7.83(d,J=8.0Hz,1H), 7.95(d,J=8.4Hz,2H), 8.10(d,J=8.0Hz,2H), 8.32(d,J=8.8Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/IPE, to give the title compound as a pale brown powder.

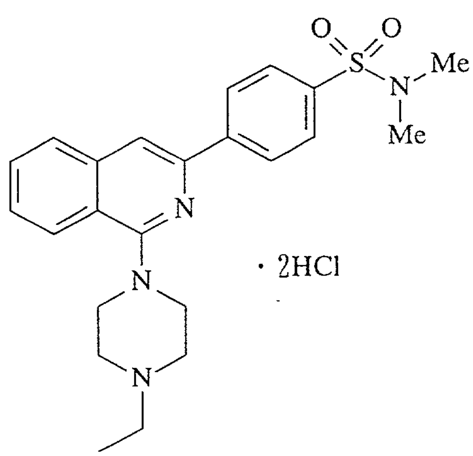
Hydrochloride:

m.p.; 170-172°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 2.46(br-d,3H), 3.20-3.27(m,2H), 3.32-3.40(m,2H), 3.56(br-t,2H), 3.63(br-d,2H), 4.03(br-d,2H), 7.57(br-s,1H), 7.67(br-t,1H), 7.79(br-t,1H), 7.91(d,J=8.4Hz,2H), 8.04(d,J=8.0Hz,1H), 8.16(d,J=8.0Hz,1H), 8.24(s,1H), 8.42(d,J=8.4Hz,2H), 11.11(br-s,1H).

MS(FAB) m/z 411(M+H)$^+$.

Example 362 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(N,N-dimethylsulfamoyl)phenyl]isoquinoline dihydrochloride



N,N-Dimethyl-4-tributylstannylbenzenesulfonamide (1.21 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.55 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.10 g) in xylene in nitrogen atmosphere overnight. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid, and the resulting aqueous layer was washed with ethyl acetate. Then, it was adjusted to pH 10 by a 8N aqueous solution of sodium hydroxide, extracted with ethyl acetate, washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.51 g of the free compound of the title compound as a pale brown amorphous.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.57(q,J=7.2Hz,2H), 2.75(s,6H), 2.77(br-t,4H), 3.61(br-t,4H), 7.53(br-t,1H), 7.64(br-t,1H), 7.78(s,1H), 7.87(d,J=8.8Hz,2H), 8.11(br-d,1H), 8.34(d,J=8.8Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a pale brown powder.

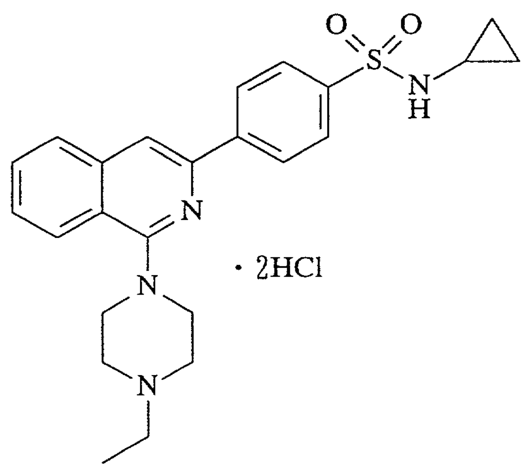
Hydrochloride:

m.p.; 155-156°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 2.66(s,6H), 3.21-3.27(m,2H), 3.33-3.40(m,2H), 3.54(br-t,2H), 3.63(br-d,2H), 4.03(br-d,2H), 7.68(br-t,2H), 7.80(br-t,2H), 7.88(d,J=8.6Hz,2H), 8.05(d,J=8.4Hz,1H), 8.28(s,1H), 8.46(d,J=8.6Hz,2H), 10.97(br-s,1H).

MS(FAB) m/z 425(M+H)$^+$.

Example 363 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(N-cyclopropylsulfamoyl)phenyl]isoquinoline dihydrochloride



N-Cyclopropyl-4-tributylstannylbenzenesulfonamide (1.00 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.56 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.08 g) in xylene in nitrogen atmosphere overnight. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid, and the resulting aqueous layer was washed with ethyl acetate. Then, it was adjusted to pH 10 by a 8N aqueous solution of sodium

hydroxide, extracted with ethyl acetate, washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.43 g of the free compound of the title compound as a pale brown amorphous.

Free compound:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.39-0.52(m,4H), 1.08(t,J=7.2Hz,3H), 2.15(br-s,1H), 2.68(br-t,4H), 3.47(br-t,4H), 7.62(br-t,1H), 7.74(br-t,1H), 7.92(d,J=8.6Hz,2H), 7.96-7.99(m,2H), 7.10(d,J=8.0Hz,1H), 8.13(s,1H), 8.42(d,J=8.6Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/IPE, to give the title compound as a pale brown powder.

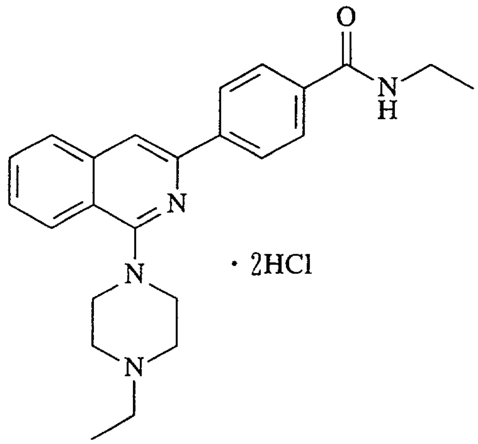
Hydrochloride:

m.p.; 158-159.5°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.39-0.53(m,4H), 1.34(t,J=7.2Hz,3H), 2.16(br-s,1H), 3.20-3.27(m,2H), 3.32-3.40(m,2H), 3.56(br-t,2H), 3.63(br-d,2H), 4.04(br-d,2H), 7.67(br-t,1H), 7.80(br-t,1H), 7.94(d,J=8.4Hz,2H), 8.00-8.05(m,2H), 8.16(d,J=8.6Hz,1H), 8.25(s,1H), 8.43(d,J=8.6Hz,2H), 11.14(br-s,1H).

MS(FAB) m/z 437$(M+H)^{+}$.

Example 364 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(N-ethylcarbamoyl)phenyl]isoquinoline dihydrochloride



· 2HCl

N-Ethyl-4-tributylstannylbenzamide (1.35 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.82 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.12 g) in xylene in nitrogen atmosphere overnight. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid, and the resulting aqueous layer was washed with ethyl acetate. Then, it was adjusted to pH 10 by a 8N aqueous solution of sodium hydroxide, extracted with ethyl acetate, washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.58 g of the free compound of the title compound as a pale yellow powder.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H),

1.29(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.77(br-t,4H), 3.54(dq,J=5.6,7.2Hz,2H), 3.60(br-t,4H), 6.14(br-t,1H), 7.50(br-t,1H), 7.61(br-t,1H), 7.75(s,1H), 7.82(d,J=8.0Hz,1H), 7.86(d,J=8.8Hz,2H), 8.09(d,J=8.4Hz,1H), 8.24(d,J=8.8Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/IPE, to give the title compound as a pale brown powder.

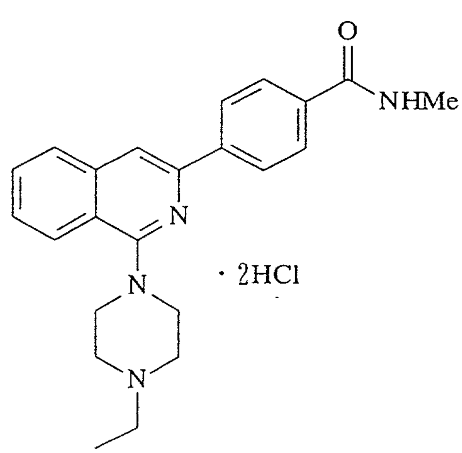
Hydrochloride:

m.p.; 160-160.5°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.16(t,J=7.2Hz,3H), 1.34(t,J=7.2Hz,3H), 3.20-3.27(m,2H), 3.29-3.40(m,2H), 3.55(br-t,2H), 3.63(br-d,2H), 4.02(br-d,2H), 7.64(br-t,1H), 7.77(br-t,1H), 7.99(d,J=8.4Hz,2H), 8.02(d,J=8.0Hz,1H), 8.14(d,J=8.4Hz,1H), 8.21(s,1H), 8.29(d,J=8.4Hz,2H), 8.59(t,J=5.4Hz,1H), 11.07(br-s,1H).

MS(FAB) m/z 389$(M+H)^+$.

<u>Example 365 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(N-methylcarbamoyl)phenyl]isoquinoline dihydrochloride</u>



N-Methyl-4-tributylstannylbenzamide (1.35 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.82 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.12 g) in xylene in nitrogen atmosphere overnight. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid, and the resulting aqueous layer was washed with ethyl acetate. Then, it was adjusted to pH 10 by a 8N aqueous solution of sodium hydroxide, extracted with ethyl acetate, washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.58 g of the title compound as a pale yellow powder.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.57(q,J=7.2Hz,2H), 2.77(br-t,4H), 3.05(s,1.5H), 3.06(s,1.5H), 3.60(br-t,4H), 6.21(br-q,1H), 7.49(br-t,1H), 7.61(br-t,1H), 7.75(s,1H), 7.80(d,J=8.4Hz,1H), 7.86(d,J=8.4Hz,2H), 8.09(d,J=8.4Hz,1H), 8.23(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/IPE, to give the title compound as a pale brown powder.

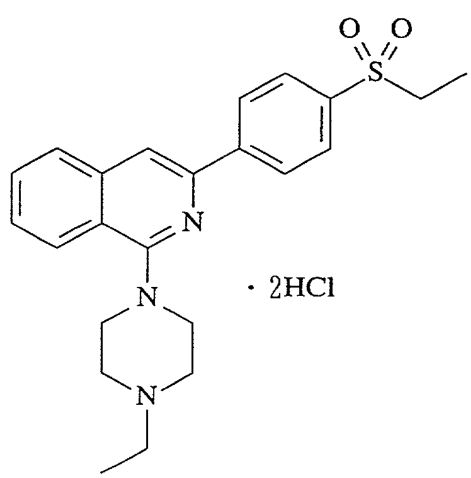
Hydrochloride:

m.p.; 161.5-163°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 2.82(s,1.5H), 2.83(s,1.5H), 3.21-3.27(m,2H), 3.32-3.40(m,2H), 3.53(br-t,2H), 3.64(br-d,2H), 4.02(br-d,2H), 7.65(br-t,1H), 7.77(br-t,1H), 7.98(d,J=8.4Hz,2H), 8.02(d,J=7.6Hz,1H), 8.14(d,J=8.4Hz,1H), 8.21(s,1H), 8.29(d,J=8.4Hz,2H), 8.55(br-q,1H), 10.90(br-s,1H).

MS(FAB) m/z 375(M+H)$^+$.

Example 366 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(ethylsulfonyl)phenyl]isoquinoline dihydrochloride



Ethyl (4-tributylstannylphenyl)sulfone (1.53 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.71 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.13 g) in xylene in nitrogen atmosphere overnight. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid, and the resulting aqueous layer was washed with ethyl acetate. Then,

it was adjusted to pH 10 by a 8N aqueous solution of sodium hydroxide, extracted in ethyl acetate, washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.68 g of the free compound of the title compound as a pale brown amorphous.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.32(t,J=7.2Hz,3H), 2.57(q,J=7.2Hz,2H), 2.77(br-t,4H), 3.16(q,J=7.2Hz,2H), 3.61(br-t,4H), 7.53(br-t,1H), 7.64(br-t,1H), 7.79(s,1H), 7.84(d,J=8.0Hz,1H), 7.99(d,J=8.4Hz,2H), 8.11(d,J=8.4Hz,1H), 8.36(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/IPE, to give the title compound as a yellow powder.

Hydrochloride:

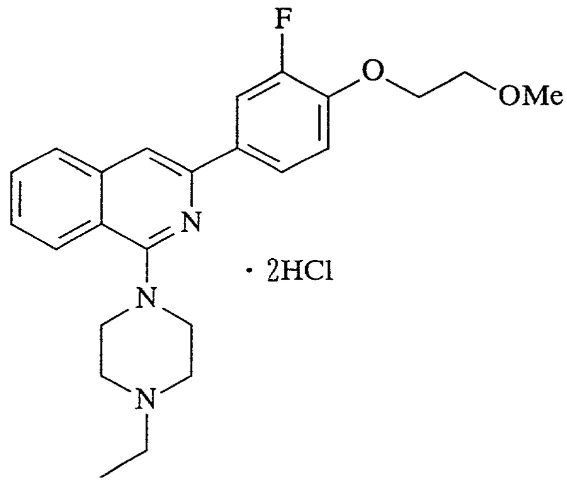
m.p.; 150-151.5°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.14(t,J=7.2Hz,3H), 1.34(t,J=7.2Hz,3H), 3.20-3.27(m,2H), 3.32-3.40(m,4H), 3.55(br-t,2H), 3.63(br-d,2H), 4.04(br-d,2H), 7.68(br-t,1H), 7.80(br-t,1H), 8.01(d,J=8.4Hz,2H), 8.05(d,J=8.0Hz,1H), 8.16(d,J=8.4Hz,1H), 8.29(s,1H), 8.47(d,J=8.4Hz,2H), 11.07(br-s,1H).

MS(FAB) m/z 410$(M+H)^+$.

Example 367 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(3-

fluoro-4-methoxyethoxyphenyl)isoquinoline dihydrochloride



4-Benzyloxy-3-fluorophenylboric acid (1.97 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (2.57 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.09 g) in toluene (250 ml) and a 10% aqueous solution of sodium carbonate (150 ml) in nitrogen atmosphere for 2 hr. 4-Benzyloxy-3-fluorophenylboric acid (0.99 g) was additionally added thereto, and the mixture was heated under reflux for 30 min. 4-Benzyloxy-3-fluorophenylboric acid (1.43 g) was again added thereto, and the mixture was heated under reflux overnight. The organic layer was separated and extracted with 2N hydrochloric acid twice, and the resulting aqueous layer was washed with ethyl acetate. Then, it was adjusted to pH 10 by a 8N aqueous solution of sodium hydroxide, extracted with ethyl acetate, washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column

chromatography (chloroform/methanol system), to give obtain 1-(4-ethylpiperazin-1-yl)-3-(4-benzyloxy-3-fluorophenyl)isoquinoline (3.19 g) as a brown viscous oil.

The resulting 1-(4-ethylpiperazin-1-yl)-3-(4-benzyloxy-3-fluorophenyl)isoquinoline (3.19 g) was converted into a hydrochloride in a conventional manner. The resulting hydrochloride was dissolved in methanol (200 ml), followed by the addition of 10% palladium/carbon catalyst (0.31 g), and the catalytic reduction was conducted at atmospheric pressure for 3 days. The catalyst was filtered off, while the solvent was evaporated. Water was added to the resulting residue, followed by the addition of an aqueous solution of saturated sodium bicarbonate, and then the mixture was extracted with chloroform. The extract was washed with brine and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give obtain 1-(4-ethylpiperazin-1-yl)-3-(3-fluoro-4-hydroxyphenyl)isoquinoline (1.01 g) as a pale brown viscous oil.

Sodium hydride (0.03 g) was washed with n-hexane, suspended in N,N-dimethylformamide (2 ml) and stirred under ice-cooling. To the resulting mixture was added the resulting 1-(4-ethylpiperazin-1-yl)-3-(3-fluoro-4-hydroxyphenyl)isoquinoline (0.20 g) dissolved in N,N-dimethylformamide (2 ml), and the mixture was stirred at room

temperature for 50 min. The mixture was again ice-cooled, followed by the addition of 2-methoxyethyl bromide (79 ml), and the mixture was stirred in nitrogen atmosphere at 50°C overnight. Water was added to the reaction solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.16 g of the free compound of the title compound as a pale brown viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.75(br-t,4H), 3.47(s,3H), 3.58(br-t,4H), 3.79-3.82(m,2H), 4.24-4.26(m,2H), 7.06(dd,J=8.6,8.6Hz,1H), 7.45(br-t,1H), 7.57(br-t,1H), 7.59(s,1H), 7.76(d,J=8.0Hz,1H), 7.85-7.88(m,1H), 7.95(dd,J=2.0,12.8Hz,1H), 8.06(d,J=8.4Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/IPE, to give the title compound as a pale yellowish brown powder.

Hydrochloride:

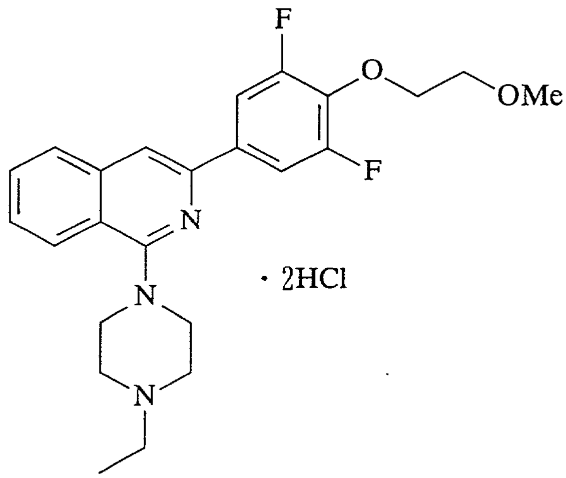
m.p.; 112.5-114°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 3.20-3.27(m,2H), 3.31-3.39(m,2H), 3.34(s,3H), 3.52(br-t,2H), 3.63(br-d,2H), 3.71-373(m,2H), 4.00(br-d,2H), 4.24-

4.26(m,2H), 7.31(dd,J=8.8,8.8Hz,1H), 7.60(br-t,1H), 7.74(br-t,1H), 7.95-8.06(m,3H), 8.08(s,1H), 8.11(d,J=8.4Hz,1H), 10.96(br-s,1H).

MS(FAB) m/z 410(M+H)$^+$.

Example 368 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(3,5-difluoro-4-methoxyethoxyphenyl)isoquinoline dihydrochloride



4-Benzyloxy-3,5-difluorophenylboric acid (1.97 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (5.20 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.50 g) in toluene (250 ml) and a 10% aqueous solution of sodium carbonate (150 ml) in nitrogen atmosphere for 1 hr. 4-Benzyloxy-3,5-difluorophenylboric acid (1.15 g) was additionally added thereto, and the mixture was heated under reflux for 1 hr. 4-Benzyloxy-3,5-difluorophenylboric acid (1.15 g) was additionally added to the resulting mixture, and then heated under reflux overnight. The organic layer was separated and extracted with 2N hydrochloric acid twice. The resulting

aqueous layer was washed with ethyl acetate, adjusted to pH 10 by a 8N aqueous solution of sodium hydroxide, extracted with ethyl acetate, washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 1-(4-ethylpiperazin-1-yl)-3-(4-benzyloxy-3,5-difluorophenyl)isoquinoline (6.44 g) as a brown viscous oil.

The resulting 1-(4-ethylpiperazin-1-yl)-3-(4-benzyloxy-3,5-difluorophenyl)isoquinoline (6.44 g) was converted into a hydrochloride in a conventional manner. The hydrochloride was dissolved in methanol (200 ml), followed by the addition of 10% palladium/carbon catalyst (0.48 g), and then the catalytic reduction was conducted at atmospheric pressure overnight. The catalyst was filtered off, while the solvent was evaporated. Water was added to the resulting residue, followed by the addition of an aqueous solution of saturated sodium bicarbonate, and the mixture was extracted with chloroform. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated, to give obtain 1-(4-ethylpiperazin-1-yl)-3-(3,5-difluoro-4-hydroxyphenyl)isoquinoline (3.36 g) as a pale brown amorphous.

Sodium hydride (0.04 g) was washed with n-hexane, suspended in N,N-dimethylformamide (2 ml) and stirred under ice-cooling. The above-described 1-(4-ethylpiperazin-1-

yl)-3-(3,5-difluoro-4-hydroxyphenyl)isoquinoline (0.30 g) dissolved in N,N-dimethylformamide (2 ml) was added thereto, and the mixture was stirred at room temperature for 50 min. The mixture was again ice-cooled, followed by the addition of 2-methoxyethyl bromide (115 ml), and the mixture was stirred in nitrogen atmosphere at 50°C overnight. Water was added to the reaction solution, and then it was extracted with ethyl acetate. The extract was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.26 g of the free compound of the title compound as a brown viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.75(br-t,4H), 3.46(s,3H), 3.56(br-t,4H), 3.74-3.76(m,2H), 4.32-4.34(m,2H), 7.47(br-t,1H), 7.57(s,1H), 7.59(br-t,1H), 7.69-7.77(m,3H), 8.06(d,J=8.0Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with methanol/ether, to give the title compound as a pale yellowish brown powder.

Hydrochloride:

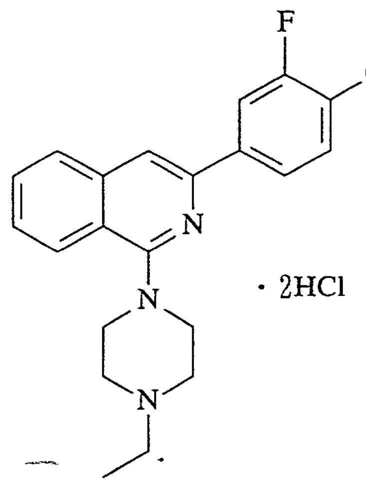
m.p.; 110-112°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 3.19-3.26(m,2H), 3.30-3.37(m,2H), 3.31(s,3H), 3.55(br-t,2H), 3.62(br-d,2H), 3.65-3.67(m,2H), 4.01(br-d,2H), 4.28-

4.30(m,2H), 7.64(br-t,1H), 7.77(br-t,1H), 7.93-7.80(m,3H), 8.13(d,J=8.4Hz,1H), 8.18(s,1H), 11.20(br-s,1H).

MS(FAB) m/z 428$(M+H)^+$.

Example 369 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[3-fluoro-4-(2-hydroxyethoxy)phenyl]isoquinoline dihydrochloride



Sodium hydride (0.08 g) was washed with n-hexane, suspended in N,N-dimethylformamide (0.5 ml) and stirred under ice-cooling, to which was then added 1-(4-ethylpiperazin-1-yl)-3-(3-fluoro-4-hydroxyphenyl)isoquinoline (0.50 g) obtained in the same manner as in Example 367 dissolved in N,N-dimethylformamide (2 ml), and the mixture was stirred at room temperature for 30 min. The mixture was again ice-cooled, followed by the addition of 2-(tert-butyldimethylsilyloxy)ethyl bromide (0.51 g) dissolved in N,N-dimethylformamide (1 ml), and the mixture was stirred in nitrogen atmosphere at 50°C overnight. Water was added to the reaction solution, and the mixture was extracted with ethyl

acetate. The extract was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give obtain 1-(4-ethylpiperazin-1-yl)-3-{3-fluoro-4-[2-(tert-butyldimethylsilyloxy)ethoxy]phenyl}isoquinoline (0.62 g) as a pale brown viscous oil.

The resulting 1-(4-ethylpiperazin-1-yl)-3-{3-fluoro-4-[2-(tert-butyldimethylsilyloxy)ethoxy]phenyl}isoquinoline (0.62 g) was dissolved in tetrahydrofuran (6 ml), to which was then added 1.0M tetrabutylammonium fluoride/tetrahydrofuran solution (1.46 ml), and the mixture was stirred for 2 hr. The solvent was evaporated, and the resulting residue was dissolved in ethyl acetate, washed with water (three times) and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.42 g of the free compound of the title compound as a yellow powder.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.76(br-t,4H), 3.58(br-t,4H), 4.02(t,J=4.4Hz,2H), 4.22(t,J=4.4Hz,2H), 7.07(dd,J=8.6,8.6Hz,1H), 7.46(br-t,1H), 7.59(br-t,1H), 7.61(s,1H), 7.78(d,J=8.4Hz,1H), 7.87-7.90(m,1H), 7.96(dd,J=2.2,13.0Hz,1H), 8.07(d,J=8.4Hz,1H).

The resulting free compound was converted into a

hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a pale yellowish brown powder.

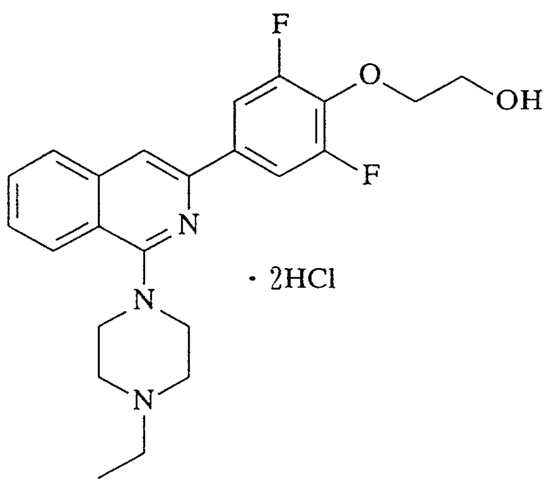
Hydrochloride:

m.p.; 119-120°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 3.20-3.27(m,2H), 3.31-3.38(m,2H), 3.52(br-t,2H), 3.63(br-d,2H), 3.77(t,J=5.0Hz,2H), 4.00(br-d,2H), 4.15(t,J=5.0Hz,2H), 7.31(dd,J=8.8,8.8Hz,1H), 7.60(br-t,1H), 7.74(br-t,1H), 7.96(d,J=8.0Hz,1H), 7.97-8.00(m,1H), 8.04(dd,J=2.0,13.2Hz,1H), 8.07(s,1H), 8.11(d,J=8.4Hz,1H), 10.93(br-s,1H).

MS(FAB) m/z 396(M+H)$^+$.

Example 370 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[3,5-difluoro-4-(2-hydroxyethoxy)phenyl]isoquinoline



Sodium hydride (0.07 g) was washed with n-hexane, suspended in N,N-dimethylformamide (0.5 ml) and stirred under ice-cooling, to which was then added 1-(4-ethylpiperazin-1-

yl)-3-(3,5-difluoro-4-hydroxyphenyl)isoquinoline (0.52 g) obtained in the same manner as in Example 368 dissolved in N,N-dimethylformamide (2 ml), and the mixture was stirred at room temperature for 50 min. The mixture was again ice-cooled, followed by the addition of 2-(tert-butyldimethylsilyloxy)ethyl bromide (0.51 g) dissolved in N,N-dimethylformamide (1 ml), and the mixture was stirred in nitrogen atmosphere at 50°C overnight. Water was added to the reaction solution, and the mixture was extracted with ethyl acetate. The extract was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 1-(4-ethylpiperazin-1-yl)-3-{3,5-difluoro-4-[2-(tert-butyldimethylsilyloxy)ethoxy]phenyl}isoquinoline (0.62 g) as a brown viscous oil.

The resulting 1-(4-ethylpiperazin-1-yl)-3-{3,5-difluoro-4-[2-(tert-butyldimethylsilyloxy)ethoxy]phenyl}isoquinoline (0.62 g) was dissolved in tetrahydrofuran (6 ml), to which was then added 1.0M tetrabutylammonium fluoride/tetrahydrofuran solution (1.41 ml), and the mixture was stirred for 75 min. The solvent was evaporated, and the resulting residue was dissolved in ethyl acetate, washed with (three times) and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column

chromatography (chloroform/methanol system), to give 0.46 g of the free compound of the title compound as a pale brown powder.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.76(br-t,4H), 3.58(br-t,4H), 3.93(t,J=4.4Hz,2H), 4.31(t,J=4.4Hz,2H), 7.49(br-t,1H), 7.60(s,1H), 7.61(br-t,1H), 7.72-7.80(m,3H), 8.08(d,J=8.4Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/ether, to give the title compound as a yellowish brown powder.

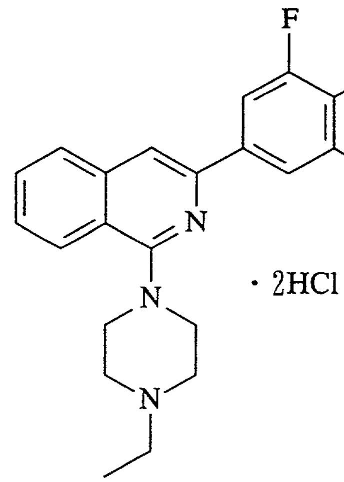
Hydrochloride:

m.p.; 112.5-114°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 3.20-3.27(m,2H), 3.30-3.38(m,2H), 3.52(br-t,2H), 3.63(br-d,2H), 3.71(d,J=5.0Hz,2H), 4.20(d,J=5.0Hz,2H), 7.64(br-t,1H), 7.77(br-t,1H), 7.92-7.99(m,3H), 8.13(d,J=8.0Hz,1H), 8.18(s,1H), 10.97(br-s,1H).

MS(FAB) m/z 414$(M+H)^+$.

Example 371 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[3,5-difluoro-4-(2-fluoroethoxy)phenyl]isoquinoline dihydrochloride



Sodium hydride (0.05 g) was washed with n-hexane, suspended in N,N-dimethylformamide (0.5 ml) and stirred under ice-cooling, to which was then added 1-(4-ethylpiperazin-1-yl)-3-(3,5-difluoro-4-hydroxyphenyl)isoquinoline (0.31 g) obtained in the same manner as in Example 368 dissolved in N,N-dimethylformamide (2 ml), and the mixture was stirred at room temperature for 35 min. The resulting mixture was again ice-cooled, followed by the addition of 2-fluoroethyl bromide (95 ml), and the mixture was stirred in nitrogen atmosphere at 50°C overnight. Water was added to the reaction solution, and the mixture was extracted with ethyl acetate extraction. The extract was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.20 g of the free compound of the title compound as a brown viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H),

2.56(q,J=7.2Hz,2H), 2.75(br-t,4H), 3.57(br-t,4H), 4.43(dt,J=4.0,28.4Hz,2H), 4.75(dt,J=4.0,47.2Hz,2H), 7.48(br-t,1H), 7.58(s,1H), 7.60(br-t,1H), 7.70-7.78(m,3H), 8.07(d,J=8.8Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a pale yellow powder.

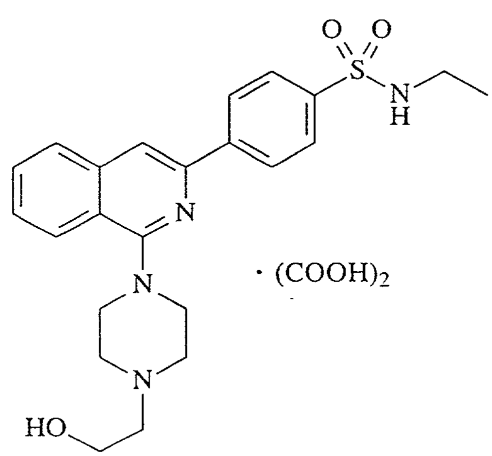
Hydrochloride:

m.p.; 105.0-105.5°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.32(t,J=7.2Hz,3H), 3.21-3.28(m,2H), 3.31-3.39(m,2H), 3.48(br-t,2H), 3.64(br-d,2H), 4.03(br-d,2H), 4.43(dt,J=3.8,30.4Hz,2H), 4.73(dt,J=3.8,48.0Hz,2H), 7.65(br-t,1H), 7.78(br-t,1H), 7.96-8.02(m,3H), 8.13(d,J=8.4Hz,1H), 8.20(s,1H), 10.57(br-s,1H).

MS(FAB) m/z 416$(M+H)^+$.

<u>Example 372 Synthesis of 1-[4-(2-hydroxyethyl)piperazin-1-yl]-3-[4-(N-ethylsulfamoyl)phenyl]isoquinoline oxalate</u>



N-Ethyl-4-tributylstannylbenzenesulfonamide (1.42 g) and 3-bromo-1-(4-formylpiperazin-1-yl)isoquinoline (0.82 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.12 g) in xylene in nitrogen atmosphere overnight. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 5N hydrochloric acid, and the resulting aqueous layer was washed with ethyl acetate. Then, it was adjusted to pH 10 by a 8N aqueous solution of sodium hydroxide, extracted with ethyl acetate, washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (toluene/acetone system), to give 1-(4-formylpiperazin-1-yl)-3-[4-(N-ethylsulfamoyl)phenyl]isoquinoline (0.45 g).

To the resulting 1-(4-formylpiperazin-1-yl)-3-[4-(N-ethylsulfamoyl)phenyl]isoquinoline (0.45 g) were added ethanol (20 ml) and a 8N aqueous solution of sodium hydroxide (651 ml), and the mixture was heated under reflux in nitrogen atmosphere for 1.5 hr. The solvent was evaporated, and to the resulting residue were added water and ethyl acetate. The organic layer was separated. Then it was washed with brine, and dried over magnesium sulfate. The solvent was evaporated, to give 1-(piperazin-1-yl)-3-[4-(N-ethylsulfamoyl)phenyl]isoquinoline (0.49 g) as a colorless

powder.

The resulting 1-(piperazin-1-yl)-3-[4-(N-ethylsulfamoyl)phenyl]isoquinoline (0.49 g) was dissolved in N,N-dimethylformamide (10 ml), followed by the addition of triethylamine (290 ml) and ethylene bromohydrin (185 ml), and the reaction mixture was reacted at 50°C overnight in nitrogen atmosphere. Water was added to the reaction solution, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water (four times) and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.20 g of the free compound of the title compound as a colorless powder.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.14(t,J=7.2Hz,3H), 2.71(t,J=5.4Hz,2H), 2.84(br-t,4H), 3.07(dq,J=6.2,7.2Hz,2H), 3.59(br-s,4H), 3.71(t,J=5.4Hz,2H), 4.30(t,J=6.2Hz,1H), 7.54(br-t,1H), 7.65(br-t,1H), 7.79(s,1H), 7.84(d,J=8.0Hz,1H), 7.96(d,J=8.6Hz,2H), 8.10(d,J=8.4Hz,1H), 8.31(d,J=8.6Hz,2H).

The resulting free compound was converted into an oxalate in a conventional manner, and then recrystallized from ethanol/IPE, to give the title compound as a colorless powder.

Oxalate:

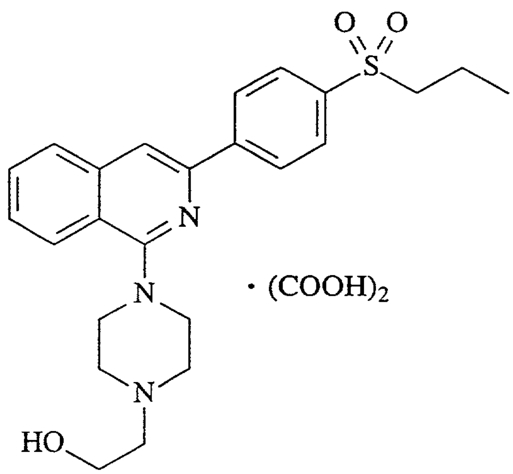
m.p.; 172-174°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.00(t,J=7.2Hz,3H), 2.79-2.86(m,2H), 2.92(br-s,2H), 3.15(br-s,4H), 3.61(br-s,4H),

3.70(t,J=7.2Hz,2H), 7.61-7.67(m,2H), 7.77(br-t,1H), 7.91(d,J=8.6Hz,2H), 8.01(d,J=8.0Hz,1H), 8.12(d,J=8.4Hz,1H), 8.18(s,1H), 8.40(d,J=8.6Hz,2H).

MS(FAB) m/z 441(M+H)$^+$.

<u>Example 373</u> <u>Synthesis of 1-[4-(2-hydroxyethyl)piperazin-1-yl]-3-[4-(propylsulfonyl)phenyl]isoquinoline oxalate</u>



Propyl-(4-tributylstannylphenyl)sulfone (1.59 g) and 3-bromo-1-(4-formylpiperazin-1-yl)isoquinoline (0.93 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.13 g) in xylene in nitrogen atmosphere overnight. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 5N hydrochloric acid, and the resulting aqueous layer was washed with ethyl acetate. Then, it was adjusted to pH 10 by a 8N aqueous solution of sodium hydroxide, extracted with ethyl acetate, washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the

resulting residue was purified by silica gel column chromatography (toluene/acetone system), to give 1-(4-formylpiperazin-1-yl)-3-[4-(propylsulfonyl)phenyl]isoquinoline (0.76 g).

To the resulting 1-(4-formylpiperazin-1-yl)-3-[4-(propylsulfonyl)phenyl]isoquinoline (0.72 g) were added ethanol (25 ml) and a 8N aqueous solution of sodium hydroxide (1.06 ml), and the mixture was heated under reflux in nitrogen atmosphere for 1.5 hr. The solvent was evaporated, and to the resulting residue were added water and ethyl acetate. The organic layer was separated. Then, it was washed with brine, and dried over magnesium sulfate. The solvent was evaporated, to give 1-(piperazin-1-yl)-3-[4-(propylsulfonyl)phenyl]isoquinoline (0.61 g) as a colorless powder.

The resulting 1-(piperazin-1-yl)-3-[4-(propylsulfonyl)phenyl]isoquinoline (0.61 g) was dissolved in N,N-dimethylformamide (10 ml), followed by the addition of triethylamine (401 μl) and ethylene bromohydrin (255 μl), and the resulting reaction mixture was reacted at 50°C overnight in nitrogen atmosphere. Water was added to the reaction solution, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water (four times) and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.59 g of

the free compound of the title compound as a colorless powder.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.02(t,J=7.2Hz,3H), 1.74-1.83(m,2H), 2.71(t,J=5.4Hz,2H), 2.85(br-t,4H), 3.09-3.13(m,2H), 3.59(br-s,4H), 3.71(t,J=5.4Hz,2H), 7.55(br-t,1H), 7.65(br-t,1H), 7.81(s,1H), 7.85(d,J=8.0Hz,1H), 7.99(d,J=8.4Hz,2H), 8.10(d,J=8.4Hz,1H), 8.35(d,J=8.4Hz,2H).

The resulting free comopund was converted into an oxalate in a conventional manner, and then recrystallized from ethanol/IPE, to give the title compound as a colorless powder.

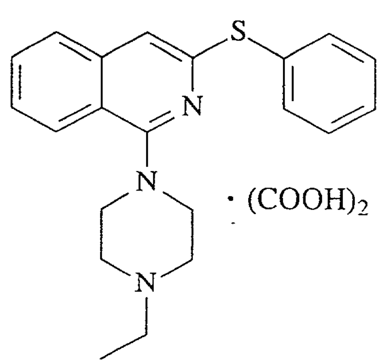
Oxalate:

m.p.; 127-129°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.94(t,J=7.2Hz,3H), 1.55-1.64(m,2H), 3.04(br-s,2H), 3.27(br-s,4H), 3.31-3.35(m,2H), 3.66(br-s,4H), 3.73(t,J=5.6Hz,2H), 7.66(br-t,1H), 7.78(br-t,1H), 8.01(d,J=8.4Hz,2H), 8.03(br-d,1H), 8.14(d,J=8.4Hz,1H), 8.24(s,1H), 8.46(d,J=8.4Hz,2H).

MS(FAB) m/z 440$(M+H)^+$.

<u>Example 374 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(phenylthio)isoquinoline oxalate</u>



3-Bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.51 g) was dissolved in tetrahydrofuran (20 ml) and cooled to -78°C in nitrogen atmosphere. To the mixture was added dropwise 2.5M (n-butyl)lithium/hexane solution (0.73 ml), and the mixture was further stirred for 1 hr. Subsequently, diphenyl disulfide (0.40 g) dissolved in tetrahydrofuran (10 ml) was added thereto, and the temperature was raised to room temperature under stirring overnight. Water was added thereto, and the mixture was extracted with ethyl acetate. The extract was washed with a 2N aqueous solution of sodium hydroxide (three times) and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (toluene/acetone system), to give 0.35 g of the free compound of the title compound as a yellow viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.14(t,J=7.2Hz,3H), 2.51(q,J=7.2Hz,2H), 2.65(br-t,4H), 3.46(br-t,4H), 6.87(s,1H), 7.34-7.66(m,8H), 7.96(d,J=8.0Hz,1H).

The resulting free compound was converted into an oxalate in a conventional manner, and then recrystallized from ethanol/IPE, to give the title compound as a colorless powder.

Oxalate:

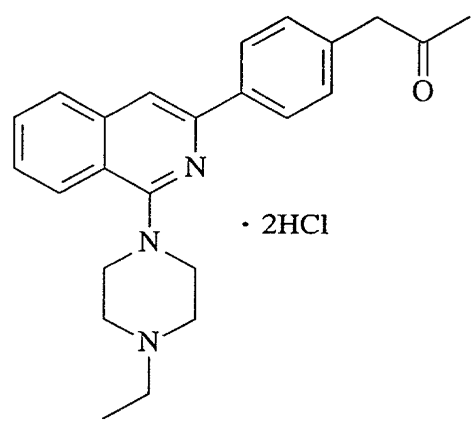
m.p.; 181.5-183°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.22(t,J=7.2Hz,3H), 3.02-3.09(m,2H), 3.22(br-s,4H), 3.53(br-s,4H), 7.44-7.79(m,9H),

8.02(d,J=8.4Hz,1H).

MS(FAB) m/z 350(M+H)$^+$.

Example 375 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(2-oxopropyl)phenyl]isoquinoline dihydrochloride



(4-Tributylstannyl)phenyl acetone (2.23 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.41 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.21 g) in xylene in nitrogen atmosphere overnight. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid, and the aqueous layer was washed with ethyl acetate. Then, it was adjusted to pH 10 by a 8N aqueous solution of sodium hydroxide, extracted with ethyl acetate, washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (toluene/acetone system), to give 0.97 g of the free compound of the title compound as a pale brown amorphous.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.19(s,3H), 2.56(q,J=7.2Hz,2H), 2.76(br-t,4H), 3.59(br-t,4H), 3.75(s,2H), 7.31(d,J=8.4Hz,2H), 7.47(br-t,1H), 7.59(br-t,1H), 7.69(s,1H), 7.79(d,J=8.0Hz,1H), 8.08(d,J=8.0Hz,1H), 8.15(d,J=7.2Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with methanol/IPE, to give the title compound as a yellow powder.

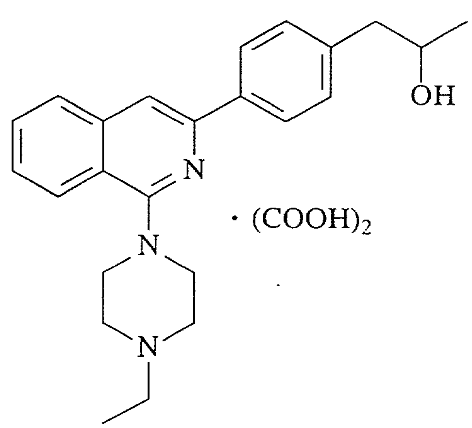
Hydrochloride:

m.p.; 125-126°C

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.32(t,J=7.2Hz,3H), 2.17(s,3H), 3.21-3.28(m,2H), 3.31-3.40(m,2H), 3.49(br-t,2H), 3.63(br-d,2H), 3.84(s,2H), 4.01(br-d,2H), 7.33(d,J=8.4Hz,2H), 7.61(br-t,1H), 7.75(br-t,1H), 7.99(d,J=7.6Hz,1H), 8.08(s,1H), 8.13-8.16(m,3H), 10.59(br-s,1H).

MS(FAB) m/z 374(M+H)$^+$.

<u>Example 376 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxypropyl)phenyl]isoquinoline oxalate</u>



1-(4-Ethylpiperazin-1-yl)-3-[4-(2-oxopropyl)phenyl]isoquinoline (0.27 g) obtained in the previous Example was dissolved in methanol (40 ml), to which was then gradually added sodium borohydride. The disappearance of the starting material was confirmed by TLC; and then, the solvent was evaporated. Water was added to the resulting mixture, and then the mixture was extracted with ethyl acetate. The resulting product was washed with brine, and dried over magnesium sulfate. The solvent was evaporated, to give 0.25 g of the free compound of the title compound as a colorless viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.0Hz,3H), 1.29(d,J=6.0Hz,3H), 2.57(q,J=7.2Hz,2H), 2.73-2.78(m,5H), 2.86(dd,J=4.6,13.4Hz,1H), 3.60(br-t,4H), 4.04-4.13(m,1H), 7.32(d,J=8.4Hz,2H), 7.46(br-t,1H), 7.59(br-t,1H), 7.68(s,1H), 7.79(d,J=8.0Hz,1H), 8.08(d,J=8.4Hz,1H), 8.13(d,J=8.4Hz,2H).

The resulting free compound was converted into an oxalate in a conventional manner, and then reprecipitated with ethanol/IPE, to give the title compound as a pale brown powder.

Hydrochloride:

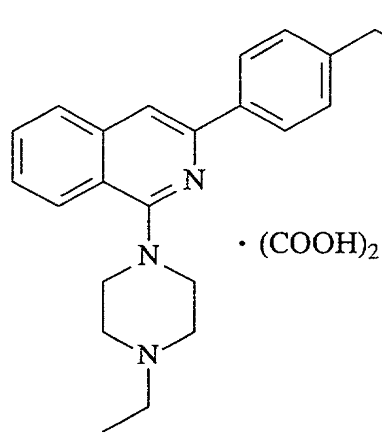
m.p.; 174-176°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.07(d,J=6.4Hz,3H), 1.26(t,J=7.2Hz,3H), 2.63(dd,J=6.2,13.4Hz,1H), 2.76(dd,J=6.6,13.4Hz,1H), 3.15(br-q,2H), 3.39(br-s,4H), 3.67(br-s,4H), 3.83-3.91(m,1H), 7.33(d,J=8.4Hz,2H),

7.59(br-t,1H), 7.73(br-t,1H), 7.97(d,J=8.0Hz,1H), 8.03(s,1H), 8.09-8.12(m,3H).

MS(FAB) m/z 376$(M+H)^+$.

<u>Example 377 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxy-2-methylpropyl)phenyl]isoquinoline oxalate</u>



1-(4-Ethylpiperazin-1-yl)-3-[4-(2-oxopropyl)phenyl]isoquinoline (0.27 g) obtained in Example 375 was dissolved in tetrahydrofuran (10 ml), and the mixture was stirred under ice-cooling. To the resulting mixture was added 3.0M methylmagnesium bromide/ether solution (0.44 ml), and the resulting mixture was further stirred for 20 min. Then, an aqueous solution of ammonium chloride and ethyl acetate were added thereto, and the mixture was stirred, to separate the organic layer. The resulting organic layer was washed with brine, dried over magnesium sulfate and the solvent was evaporated, to give 0.25 g or the free compound of the title compound as a pale brown amorphous.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.28(s,6H),

2.56(q,J=7.2Hz,2H), 2.77(br-t,4H), 2.84(s,2H), 3.60(br-t,4H), 7.32(d,J=8.2Hz,2H), 7.46(br-t,1H), 7.59(br-t,1H), 7.69(s,1H), 7.79(d,J=8.4Hz,1H), 8.08(d,J=8.4Hz,1H), 8.13(d,J=8.2Hz,2H).

The resulting free compound was converted into an oxalate in a conventional manner, and then reprecipitated with ethanol/IPE, to give the title compound as a pale brown powder.

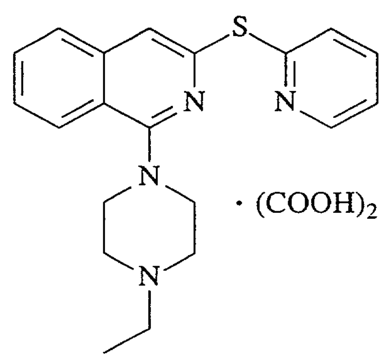
Oxalate:

m.p.; 184-186°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.10(s,6H), 1.26(t,J=7.2Hz,3H), 2.17(s,2H), 3.12-3.18(m,2H), 3.39(br-s,4H), 3.67(br-s,4H), 7.34(d,J=8.0Hz,2H), 7.59(br-t,1H), 7.73(br-t,1H), 7.97(d,J=7.6Hz,1H), 8.04(s,1H), 8.08-8.12(m,3H).

MS(FAB) m/z 390(M+H)$^{+}$.

<u>Example 378 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(2-pyridylthio)isoquinoline oxalate</u>



3-Bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.44 g) was dissolved in tetrahydrofuran (20 ml), and the mixture was cooled to -78°C in nitrogen atmosphere. To the resulting mixture was added dropwise 2.5M-(n-butyl)lithium/hexane solution (0.57 ml), and the mixture was further stirred for 30

min. Subsequently, di(2-pyridyl)disulfide (0.31 g) dissolved in tetrahydrofuran (5 ml) was added to the resulting mixture, of which the temperature was raised to room temperature under overnight stirring. Water was added thereto, and the mixture was extracted with ethyl acetate extraction. The resulting extract was washed with a 2N aqueous solution of sodium hydroxide (three times) and brine sequentially, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (toluene/acetone system), to give 0.05 g of the free compound of the title compound as a yellow viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.14(t,J=7.2Hz,3H), 2.51(q,J=7.2Hz,2H), 2.65(br-t,4H), 3.46(br-t,4H), 7.09(ddd,J=1.1,4.9,7.5Hz,1H), 7.39-7.41(m,1H), 7.46-7.61(m,4H), 7.66(d,J=8.0Hz,1H), 8.03(d,J=8.4Hz,1H), 8.49-8.51(m,1H).

The resulting free compound was converted into an oxalate in a conventional manner, and then recrystallized from ethanol/IPE, to give the title compound as a colorless powder.

Oxalate:

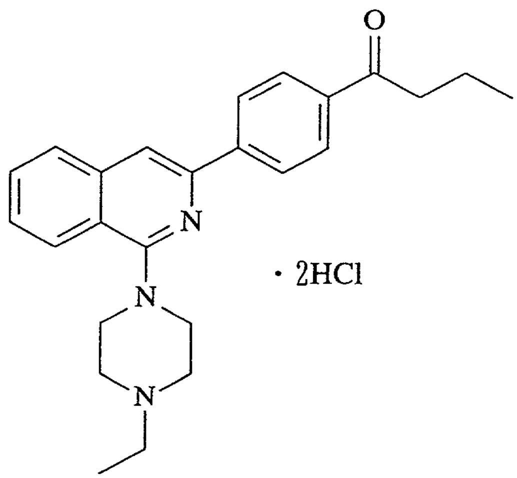
m.p.; 178-181°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.20(t,J=7.2Hz,3H), 3.02(br-s,2H), 3.20(br-s,4H), 3.51(br-s,4H), 7.25(ddd,J=0.8,4.9,7.4Hz,1H), 7.34(ddd,J=0.8,0.8,7.4Hz,1H), 7.65(br-t,1H), 7.70-7.78(m,2H), 7.71(s,1H),

7.90(d,J=8.8Hz,1H), 7.10(d,J=8.0Hz,1H), 8.47-8.49(m,1H).

MS(FAB) m/z 351$(M+H)^+$.

<u>Example 379</u> <u>Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(4-butyrylphenyl)isoquinoline dihydrochloride</u>



(n-Propyl)[(4-tributylstannyl)phenyl]ketone (1.57 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.99 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium (0) (0.14 g), in xylene in nitrogen atmosphere overnight. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The resulting filtrate was extracted with 2N hydrochloric acid. The resulting aqueous layer was washed with ethyl acetate, adjusted to pH 10 with a 8N aqueous solution of sodium hydroxide, and then extracted with ethyl acetate. The resulting organic layer was washed with a 10% sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (toluene/acetone system), to give 0.84 g of the

free compound of the title compound as a pale brown amorphous.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.04(t,J=7.2Hz,3H), 1.18(t,J=7.2Hz,3H), 1.81(tq,J=7.2,7.2Hz,2H), 2.56(q,J=7.2Hz,2H), 2.77(br-t,4H), 3.00(t,J=7.2Hz,2H), 3.61(br-t,4H), 7.51(br-t,1H), 7.62(br-t,1H), 7.78(s,1H), 7.83(d,J=8.0Hz,1H), 8.06(d,J=8.4Hz,2H), 8.10(d,J=8.4Hz,1H), 8.26(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with methanol/IPE, to give the title compound as a yellow powder.

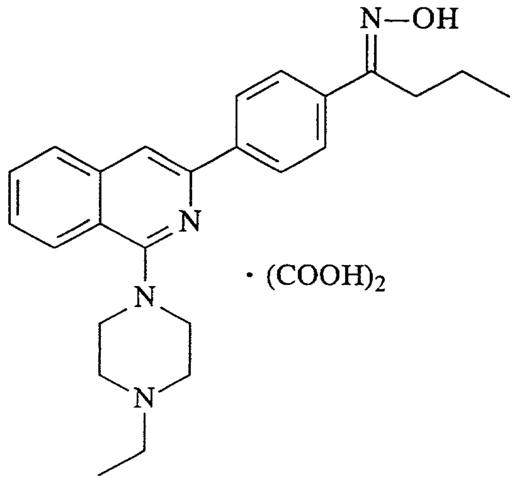
Hydrochloride:

m.p.; 110-112.5°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.96(t,J=7.2Hz,3H), 1.34(t,J=7.2Hz,3H), 1.68(tq,J=7.2,7.2Hz,2H), 3.06(t,J=7.2Hz,2H), 3.20-3.29(m,2H), 3.32-3.40(m,2H), 3.55(br-t,2H), 3.63(br-d,2H), 4.03(br-d,J=7.2Hz,2H), 7.66(br-t,1H), 7.79(br-t,1H), 8.04(d,J=8.0Hz,1H), 8.10(d,J=8.4Hz,2H), 8.15(d,J=8.4Hz,1H), 8.25(s,1H), 8.35(d,J=8.4Hz,2H), 11.03(br-s,1H).

MS(FAB) m/z 388$(M+H)^+$.

Example 380 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(1-hydroxyiminobutyl)phenyl]isoquinoline



1-(4-Ethylpiperazin-1-yl)-3-(4-butyrylphenyl)isoquinoline (0.27 g) obtained in the previous Example was dissolved in ethanol (40 ml), to which was then added a solution of hydroxylamine hydrochloride (0.14 g) and sodium acetate (0.22 g) dissolved in water (10 ml), and the mixture was heated under reflux. The solvent was evaporated, and the resulting residue was purified by NH-silica gel column chromatography (ethyl acetate/methanol system), to give 0.23 g of the free compound of the title compound as a pale brown amorphous.

Free compound:

^{1}H-NMR(400MHz,CDCl$_3$); δ (ppm) 1.00(t,J=7.2Hz,3H), 1.19(t,J=7.2Hz,3H), 1.60-1.67(m,4H), 2.59(q,J=7.2Hz,2H), 2.79-2.85(m,6H), 3.63(br-t,4H), 7.47(br-t,1H), 7.60(Br-t,1H), 7.72-7.75(m,2H), 7.80(br-d,1H), 8.08(br-d,1H), 8.18-8.21(m,2H), 8.32(br-s,1H).

The resulting free compound was converted into an oxalate in a conventional manner, and then recrystallized from

methanol/IPE, to give the title compound as a colorless powder.

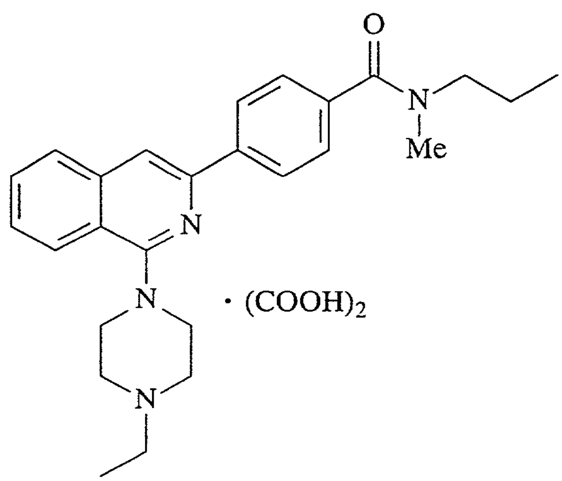
Oxalate:

m.p.; 179.5-180°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.94(t,J=7.2Hz,3H), 1.26(t,J=7.2Hz,3H), 1.47-1.57(m,2H), 2.76(br-t,2H), 3.11(br-q,2H), 3.35(br-s,4H), 3.67(br-s,4H), 7.62(br-t,1H), 7.75(br-t,1H), 7.78(d,J=8.4Hz,2H), 8.00(d,J=8.0Hz,1H), 8.11(s,1H), 8.12(d,J=8.4Hz,1H), 8.22(d,J=8.4Hz,2H), 11.19(br-s,1H).

MS(FAB) m/z 403(M+H)$^+$.

<u>Example 381 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(N-methyl-N-propylcarbamoyl)phenyl]isoquinoline</u>



N-Methyl-N-propyl-4-tributylstannylbenzamide (2.36 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.02 g) were heated under reflux overnight in the presence of tetrakistriphenylphosphinepalladium(0) (0.15 g) in xylene in nitrogen atmosphere. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was

extracted with 2N hydrochloric acid. The aqueous layer was washed with ethyl acetate and adjusted to pH 10 by a 8N aqueous solution of sodium hydroxide, and then extracted with ethyl acetate, washed with a 10% aqueous solution of sodium carbonate and brine and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.72 g of the free compound of the title compound as a pale yellow powder.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.80(br-t,1.5H), 1.01(br-t,1.5H), 1.18(t,J=7.2Hz,3H), 1.56-1.75(m,2H), 2.56(q,J=7.2Hz,2H), 2.77(br-t,4H), 3.00-3.54(m,5H), 3.60(br-t,4H), 7.48(br-t,1H), 7.60(br-t,1H), 7.73(s,1H), 7.80(d,J=8.4Hz,1H), 8.09(d,J=7.6Hz,1H), 8.21(d,J=8.4Hz,2H).

The resulting free compound was converted into a oxalate in a conventional manner, and then recrystallized from ethanol/IPE, to give the title compound as a pale brown powder.

Oxalate:

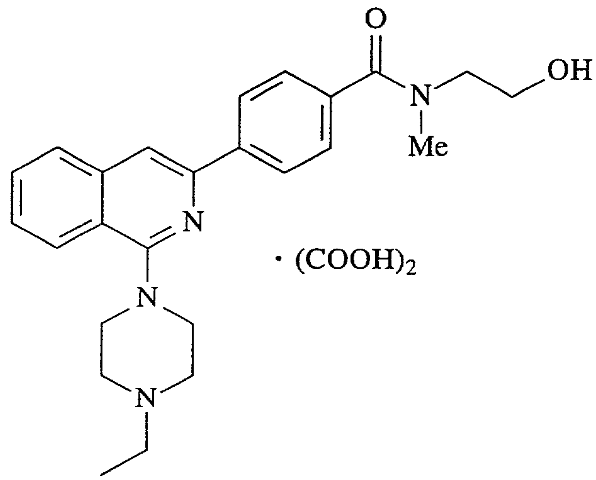
m.p.; 131-132°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.71(br-s,1.5H), 0.93(br-s,1.5H), 1.26(t,J=7.2Hz,3H), 1.51-1.67(br-d,2H), 2.94-3.66(m,15H), 7.50(br-t,t,1H), 7.76(br-t,1H), 8.01(d,J=7.6Hz,1H), 8.12-8.15(m,2H), 8.26(d,J=8.4Hz,2H).

MS(FAB) m/z 417$(M+H)^+$.

<u>Example 382</u> <u>Synthesis of 1-(4-ethylpiperazin-1-yl)-3-{4-[N-</u>

(2-hydroxyethyl)-N-methylcarbamoyl]phenyl}isoquinoline



N-Methyl-N-(2-benzyloxyethyl)-4-tributylstannylbenzamide (1.93 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.93 g) were heated under reflux overnight in the presence of tetrakistriphenylphosphinepalladium(0) (0.13 g) in xylene in nitrogen atmosphere. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid. The aqueous layer was washed with ethyl acetate and adjusted to pH 10 by a 8N aqueous solution of sodium hydroxide, which was then extracted with ethyl acetate, washed with a 10% aqueous solution of sodium carbonate and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 1-(4-ethylpiperazin-1-yl)-3-{4-[N-(2-benzyloxyethyl)-N-methylcarbamoyl]phenyl}isoquinoline (0.69 g) as a pale yellow viscous oil.

Sequentially, the resulting 1-(4-ethylpiperazin-1-yl)-3-{4-[N-(2-benzyloxyethyl)-N-methylcarbamoyl]phenyl}isoquinoline (0.69 g) was converted into a hydrochloride in a conventional manner and then dissolved in methanol (50 ml). To the resulting solution was added 10% palladium/carbon catalyst (0.20 g), and the catalytic reduction was conducted at atmospheric pressure overnight. The catalyst was filtered off, while the solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.41 g of the free compound of the title compound as a pale yellow amorphous.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.57(q,J=7.2Hz,2H), 2.77(br-t,4H), 3.13(br-s,3H), 3.60(br-t,4H), 3.77(br-s,2H), 3.94(br-s,2H), 7.49(br-t,1H), 7.57(br-d,2H), 7.61(br-t,1H), 7.74(s,1H), 7.81(d,J=8.0Hz,1H), 8.09(d,J=8.4Hz,1H), 8.22(d,J=8.0Hz,2H).

The resulting free compound was converted into an oxalate in a conventional manner, and then recrystallized from ethanol/IPE, to give the title compound as a pale brown powder.

Oxalate:

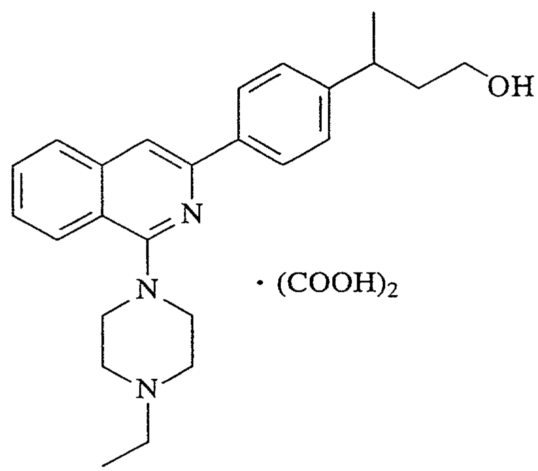
m.p.; 116-118°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.26(t,J=7.2Hz,3H), 3.01(s,3H), 3.12(br-q,2H), 3.36(br-s,6H), 3.52(br-s,2H), 3.67(br-s,4H), 7.54(d,J=8.4Hz,2H), 7.63(br-t,1H), 7.76(br-t,1H),

8.00(d,J=8.0Hz,1H), 8.12-8.14(m,2H), 8.24(br-d,2H).

MS(FAB) m/z 419$(M+H)^+$.

<u>Example 383 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxy-1-methylpropyl)phenyl]isoquinoline oxalate</u>



Ethyl 3-(4-Tributylstannylphenyl)butyrate (5.46 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.33 g) were heated under reflux overnight in the presence of tetrakistriphenylphosphinepalladium(0) (0.19 g) in xylene in nitrogen atmosphere. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid. The aqueous layer was washed with ethyl acetate, adjusted to pH 10 with a 8N aqueous solution of sodium hydroxide, and then extracted in ethyl acetate. The organic layer was washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 1-(4-ethylpiperazin-

1-yl)-3-[4-(1-ethoxycarbonylpropan-2-yl)phenyl]isoquinoline (1.34 g) as a pale yellow viscous oil.

Subsequently, the resulting 1-(4-ethylpiperazin-1-yl)-3-[4-(1-ethoxycarbonylpropan-2-yl)phenyl]isoquinoline (0.69 g) was dissolved in tetrahydrofuran (10 ml). The solution was added to a suspension of lithium aluminum hydride (0.12 g) in tetrahydrofuran (20 ml) under cooling with a cooler of sodium chloride and ice, and the mixture was stirred for another 20 min. Water (120 ml), a 5N aqueous solution of sodium hydroxide (120 ml) and water (360 ml) were added to the reaction solution in this order, and then the resulting precipitates were filtered off. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (toluene/acetone system), to give 0.32 g of the free compound of the title compound as a pale brown viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.33(d,J=7.2Hz,3H), 1.91(dt,J=7.2,7.2Hz,2H), 2.56(q,J=7.2Hz,2H), 2.76(br-t,4H), 2.96(tq,J=7.2,7.2Hz,1H), 3.55-3.66(m,6H), 7.31(d,J=8.2Hz,2H), 7.45(br-t,1H), 7.58(br-t,1H), 7.67(s,1H), 7.79(d,J=8.0Hz,1H), 8.08(d,J=8.4Hz,1H), 9.06(d,J=8.2Hz,2H).

The resulting free compound was converted into an oxalate in a conventional manner, and then recrystallized from ethanol/IPE, to give the title compound as a pale brown powder.

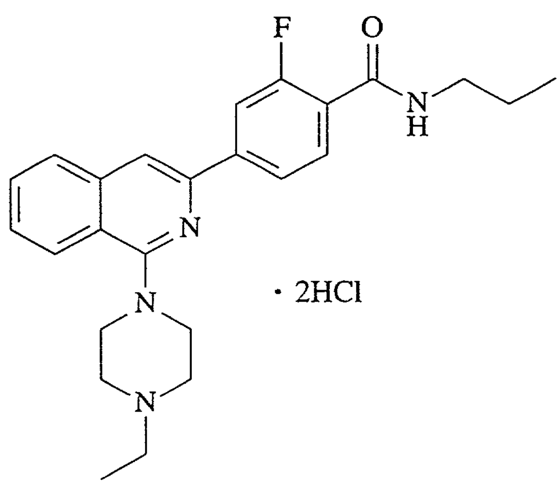
Oxalate:

m.p.; 106-108°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.24(d,J=6.8Hz,3H), 1.25(t,J=7.2Hz,3H), 1.74(br-q,2H), 2.86-2.95(m,1H), 3.11(br-s,2H), 3.28-3.38(m,6H), 3.65(br-s,4H), 7.34(d,J=8.4Hz,2H), 7.59(br-t,1H), 7.73(br-t,1H), 7.97(d,J=8.0Hz,1H), 8.03(s,1H), 8.11(br-d,3H).

MS(FAB) m/z 390(M+H)$^{+}$.

Example 384 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(N-propylcarbamoyl)-3-fluorophenyl]isoquinoline dihydrochloride



N-Propyl-3-fluoro-4-tributylstannylbenzamide (2.23 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.96 g) were heated under reflux overnight in the presence of tetrakistriphenylphosphinepalladium(0) (0.14 g) in xylene in nitrogen atmosphere. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid. The aqueous layer was washed with ethyl acetate, adjusted to pH 10 with a 8N aqueous

solution of sodium hydroxide, and then extracted with ethyl acetate. The organic layer was washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.83 g of the free compound of the title compound as a pale yellow powder.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.02(t,J=7.2Hz,3H), 1.18(t,J=7.2Hz,3H), 1.68(tq,J=7.2,7.2Hz,2H), 2.56(q,J=7.2Hz,2H), 2.77(br-t,4H), 3.46-3.51(m,2H), 3.60(br-t,4H), 6.80-6.86(m,1H), 7.52(br-t,1H), 7.63(br-t,1H), 7.75(s,1H), 7.82(d,J=8.0Hz,1H), 7.98-8.02(m,2H), 8.09(d,J=8.0Hz,1H), 8.19(dt,J=8.2Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/IPE, to give the title compound as a pale brown powder.

Hydrochloride:

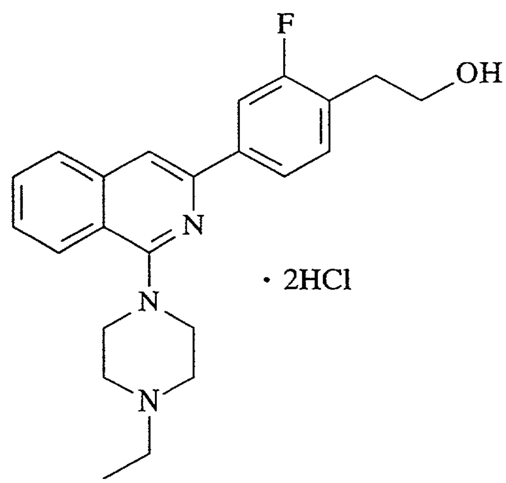
m.p.; 124-125°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.92(t,J=7.6Hz,3H), 1.33(t,J=7.2Hz,3H), 1.55(tq,J=7.2Hz,2H), 3.21-3.27(m,4H), 3.32-3.39(m,2H), 3.53(br-t,2H), 3.64(br-d,2H), 4.03(br-d,2H), 7.67(br-t,1H), 7.73(dd,J=7.8Hz,1H), 7.79(br-t,1H), 8.02(d,J=7.6Hz,1H), 8.07(br-d,1H), 8.10(dd,J=1.8,8.2Hz,1H), 8.15(d,J=8.0Hz,1H), 8.26(s,1H), 8.36(br-t,1H), 10.89(br-

s,1H).

MS(FAB) m/z 421(M+H)$^{+}$.

Example 385 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[3-fluoro-4-(2-hydroxyethyl)phenyl]isoquinoline dihydrochloride



2-(3-Fluoro-4-tributylstannylphenyl)ethyl acetate (2.77 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.19 g) were heated under reflux overnight in the presence of tetrakistriphenylphosphinepalladium(0) (0.17 g) in xylene in nitrogen atmosphere. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid. The aqueous layer was washed with ethyl acetate, adjusted to pH 10 with a 8N aqueous solution of sodium hydroxide, and then extracted with ethyl acetate. The organic layer was washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, to give a mixture (1.44 g) of 1-(4-ethylpiperazin-1-yl)-3-[3-fluoro-4-(2-

acetoxyethyl)phenyl]isoquinoline as a brown viscous oil and the starting material.

Subsequently, the resulting mixture (1.44 g) was dissolved in methanol (30 ml). A 5N aqueous solution of sodium hydroxide (11.8 ml) was added thereto, and the resulting mixture was stirred at room temperature for 2 hr. After the solvent was evaporated, water was added to the resulting residue, and then the mixture was extracted with ethyl acetate. The extract was washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (toluene/acetone system), to give 0.91 g of the free compound of the title compound as a pale yellow solid.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 3.76(br-t,4H), 2.98(t,J=6.6Hz,2H), 3.59(br-t,4H), 3.91(t,J=6.6Hz,2H), 7.33(dd,J=8.0Hz,1H), 7.48(br-t,1H), 7.60(br-t,1H), 7.66(s,1H), 7.79(d,J=8.0Hz,1H), 7.86-7.91(m,2H), 8.08(d,J=8.4Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/IPE, to give the title compound as a pale brown powder.

Hydrochloride:

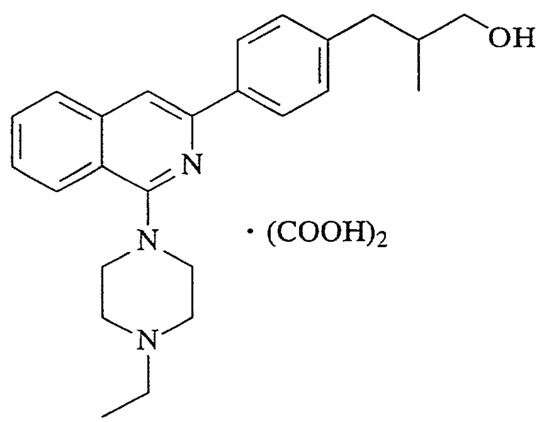
m.p.; 213-215°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H),

2.82(t,J=6.8Hz,2H), 3.20-3.27(m,2H), 3.31-3.39(m,2H), 3.51(br-t,2H), 3.63(br-d,2H), 3.65(t,J=6.8Hz,2H), 4.01(br-d,2H), 7.45(dd,J=8.0Hz,1H), 7.63(br-t,1H), 7.76(br-t,1H), 7.93-8.00(m,3H), 8.12-8.13(m,2H), 10.78(br-s,1H).

MS(FAB) m/z 380(M+H)$^+$.

Example 386 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxy-2-methylpropyl)phenyl]isoquinoline oxalate



Methyl 2-methyl-3-(4-tributylstannylphenyl)propionate (2.69 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.16 g) were heated under reflux overnight in the presence of tetrakistriphenylphosphinepalladium(0) (0.17 g) in xylene in nitrogen atmosphere. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid. The aqueous layer was washed with ethyl acetate, adjusted to pH 10 with a 8N aqueous solution of sodium hydroxide, and then extracted with ethyl acetate. The extract was washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was

purified by silica gel column chromatography (toluene/acetone system), to give obtain 1-(4-ethylpiperazin-1-yl)-3-[4-(2-methoxycarbonylpropyl)phenyl]isoquinoline (1.34 g) in pale yellow viscous oil.

Subsequently, the resulting 1-(4-ethylpiperazin-1-yl)-3-[4-(2-methoxycarbonylpropyl)phenyl]isoquinoline (1.34 g) was dissolved in tetrahydrofuran (10 ml). The solution was added to a suspension of lithium aluminum hydride (0.13 g) in tetrahydrofuran (20 ml) under cooling with a cooler of sodium chloride and ice, and the mixture was further stirred for 30 min. Water (130 ml), a 5N aqueous solution of sodium hydroxide (130 ml) and water (390 ml) were added to the reaction solution in this order, and the resulting precipitates were filtered off. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (toluene/acetone system), to give 0.62 g of the free compound of the title compound as a pale brown viscous oil.

Free compound:

^{1}H-NMR(400MHz, $CDCl_3$); δ (ppm) 0.96(d,J=6.8Hz,3H), 1.18(t,J=7.2Hz,3H), 1.96-2.05(m,1H), 2.49(dd,J=8.0,13.6Hz,1H), 2.56(q,J=7.2Hz,2H), 2.76(br-t,4H), 2.82(dd,J=6.4,13.6Hz,1H), 3.52(dd,J=6.0,10.8Hz,1H), 3.58(dd,J=6.0,10.8Hz,1H), 3.59(br-t,4H), 7.28(d,J=8.2Hz,2H), 7.45(br-t,1H), 7.58(br-t,1H), 7.68(s,1H), 7.78(d,J=7.6Hz,1H), 8.07(br-d,1H), 8.10(d,J=8.2Hz,2H).

The resulting free compound was converted into an oxalate

in a conventional manner, and then recrystallized from ethanol/IPE, to give the title compound as a pale brown powder.

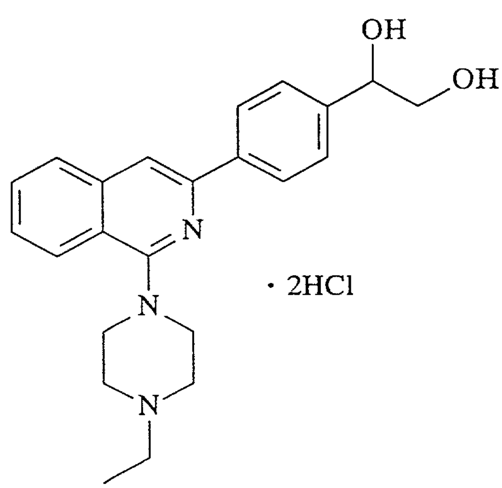
Oxalate:

m.p.; 195-196°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.82(d,J=6.8Hz,3H), 1.26(t,J=7.2Hz,3H), 1.79-1.88(m,2H), 2.35(dd,J=8.6,13.2Hz,1H), 2.78(dd,J=5.6,13.2Hz,1H), 3.12(br-q,2H), 3.26(dd,J=6.0,10.4Hz,1H), 3.31(dd,J=6.0,10.4Hz,1H), 3.36(br-s,4H), 3.66(br-s,4H), 7.30(d,J=8.0Hz,2H), 7.59(br-t,1H), 7.73(br-t,1H), 7.97(d,J=8.0Hz,1H), 8.04(s,1H), 8.11(d,J=8.0Hz,2H).

MS(FAB) m/z 390(M+H)$^+$.

Example 387 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(1,2-dihydroxyethyl)phenyl]isoquinoline dihydrochloride



2,2-Dimethyl-3-(4-tributylstannylphenyl)-1,3-dioxolane (3.64 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.05 g) were heated under reflux overnight in the presence of tetrakistriphenylphosphinepalladium(0) (0.15

g) in xylene in nitrogen atmosphere. After cooling, the reaction solution was diluted with ethyl acetate and filtered. To the filtrate was added 2N hydrochloric acid, and the mixture was stirred at room temperature for 2 hr. The aqueous layer was washed with ethyl acetate, adjusted to pH 10 with a 8N aqueous solution of sodium hydroxide, and then extracted with ethyl acetate. The extract was washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (toluene/acetone system) and then recrystallized from chloroform/n-hexane, to give 0.73 g of the free compound of the title compound as a pale brown powder.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.76(br-t,4H), 3.58(br-t,4H), 3.72(dd,J=8.0,11.2Hz,1H), 3.82(dd,J=3.6,11.2Hz,1H), 4.90(dd,J=3.6,8.0Hz,1H), 7.45-7.49(m,3H), 7.59(br-t,1H), 7.69(s,1H), 7.80(d,J=8.0Hz,1H), 8.08(d,J=8.4Hz,1H), 8.17(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/IPE, to give the title compound as a pale brown powder.

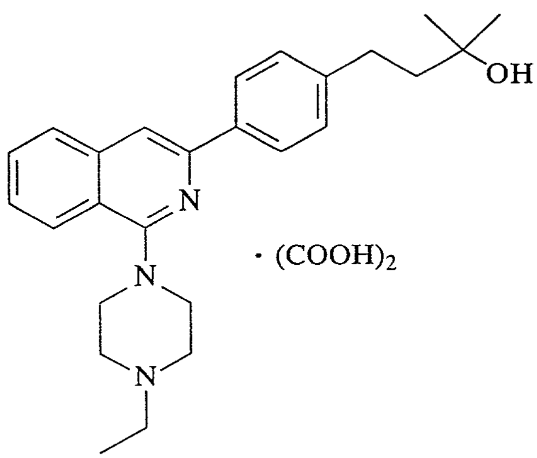
Hydrochloride:

m.p.; 132-133°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 3.20-3.27(m,2H), 3.31-3.39(m,2H), 3.48(d,J=6.0Hz,2H), 3.53(br-t,2H), 3.63(br-d,2H), 4.00(br-d,2H), 4.61(t,J=6.0Hz,1H), 7.47(d,J=8.4Hz,2H), 7.61(br-t,1H), 7.74(br-t,1H), 7.99(d,J=7.6Hz,1H), 8.07(s,1H), 8.11-8.15(m,3H), 10.94(br-s,1H).

MS(FAB) m/z 378(M+H)$^+$.

<u>Example 388 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxy-3-methylbutyl)phenyl]isoquinoline dihydrochloride</u>



4-(4-Tributylstannylphenyl)-2-butanone (2.46 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.41 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.22 g) in xylene in nitrogen atmosphere overnight. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted in 2N hydrochloric acid, and the resulting aqueous layer was washed with ethyl acetate, adjusted to pH 10 with a 8N aqueous solution of sodium hydroxide, and

then extracted with ethyl acetate. The extract was washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (toluene/acetone system), to give 1-(4-ethylpiperazin-1-yl)-3-[4-(3-oxobutyl)phenyl]isoquinoline (1.07 g) as a pale yellow viscous oil.

The resulting 1-(4-ethylpiperazin-1-yl)-3-[4-(3-oxobutyl)phenyl]isoquinoline (0.50 g) was dissolved in tetrahydrofuran (50 ml), and the mixture was stirred under ice-cooling, to which was then added 3.0M methylmagnesium bromide/ether solution (860 μl). The resulting mixture was stirred for 30 min. Then, 3.0M methylmagnesium bromide/ethyl ether solution (860 μl) was additionally added thereto, and the resulting mixture was stirred for 2 hr. An aqueous solution of saturated ammonium chloride was added to the mixture and extracted with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (toluene/acetone system), to give 0.21 g of the free compound of the title compound as a colorless viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.32(s,6H), 1.82-1.86(m,2H), 2.56(q,J=7.2Hz,2H), 2.75-2.79(m,6H), 3.59(br-t,4H), 7.31(d,J=8.0Hz,2H), 7.45(br-t,1H), 7.58(br-

t,1H), 7.67(s,1H), 7.78(d,J=8.0Hz,1H), 8.07(br-d,1H), 8.09(d,J=8.0Hz,2H).

The resulting free compound was converted into an oxalate in a conventional manner, and then recrystallized from ethanol/IPE, to give the title compound as a pale brown powder.

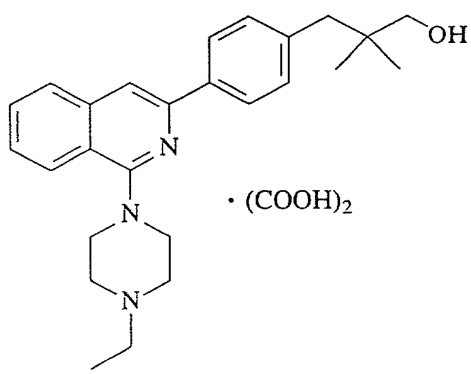
Oxalate:

m.p.; 205-206°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.17(s,6H), 1.26(t,J=7.2Hz,3H), 1.66-1.70(m,2H), 2.66-2.70(m,2H), 3.12(br-q,2H), 3.36(br-s,4H), 3.66(br-s,4H), 7.33(d,J=8.0Hz,2H), 7.59(br-t,1H), 7.73(br-t,1H), 7.97(d,J=8.0Hz,1H), 8.03(s,1H), 8.09-8.12(m,3H).

MS(FAB) m/z 404(M+H)$^+$.

Example 389 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxy-2,2-dimethylpropyl)phenyl]isoquinoline oxalate



Methyl 2,2-dimethyl-3-(4-tributylstannylphenyl)propionate (2.81 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.18 g) were heated under reflux overnight in the presence of tetrakistriphenylphosphinepalladium(0) (0.17 g) in xylene in

nitrogen atmosphere. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid, and the resulting aqueous layer was washed with ethyl acetate, adjusted to pH 10 with a 8N aqueous solution of sodium hydroxide, and then extracted with ethyl acetate. The extract was washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (toluene/acetone system), to give 1-(4-ethylpiperazin-1-yl)-3-[4-(2-methoxycarbonyl-2-methylpropyl)phenyl]isoquinoline (1.51 g) as a brown viscous oil.

The resulting 1-(4-ethylpiperazin-1-yl)-3-[4-(2-methoxycarbonyl-2-methylpropyl)phenyl]isoquinoline (1.51 g) was dissolved in tetrahydrofuran (10 ml). The solution was added to a suspension of lithium aluminum hydride (0.14 g) in tetrahydrofuran (20 ml) under cooling with a cooler of sodium chloride and ice, and the mixture was stirred for another 30 min. To the resulting solution were sequentially added water (140 ml), a 5N aqueous solution of sodium hydroxide (140 ml) and water (420 ml), and the resulting precipitates were filtered off. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (toluene/acetone system), to give 0.90 g of the free compound of the title compound as a pale brown viscous oil.

Free compound:

^{1}H-NMR(400MHz,CDCl$_3$); δ (ppm) 0.93(s,6H), 1.18(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.64(s,2H), 2.76(br-t,4H), 3.36(s,2H), 3.60(br-t,4H), 7.27(d,J=8.0Hz,2H), 7.45(br-t,1H), 7.58(br-t,1H), 7.68(s,1H), 7.79(d,J=8.0Hz,1H), 8.08(br-d,1H), 8.09(d,J=8.0Hz,2H).

The resulting free compound was converted into an oxalate in a conventional manner, and then recrystallized from ethanol/IPE, to give the title compound as a pale brown powder.

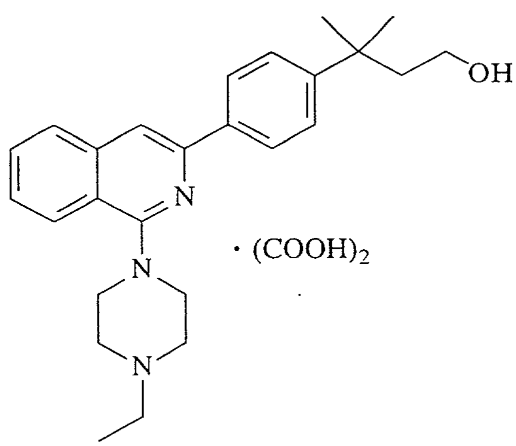
Oxalate:

m.p.; 194-195°C

^{1}H-NMR(400MHz,DMSO-d$_6$); δ (ppm) 0.80(s,6H), 1.26(t,J=7.2Hz,3H), 2.56(s,2H), 3.10-3.16(m,2H), 3.12(s,2H), 3.38(br-s,4H), 3.68(br-s,4H), 7.28(d,J=8.0Hz,2H), 7.59(br-t,1H), 7.73(br-t,1H), 7.97(d,J=8.0Hz,1H), 8.04(s,1H), 8.10(d,J=8.0Hz,2H), 8.11(br-d,1H).

MS(FAB) m/z 404(M+H)$^+$.

<u>Example 390 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[3,5-difluoro-4-(2-hydroxyethoxy)phenyl]isoquinoline oxalate</u>



3-Methyl-3-(4-tributylstannylphenyl)butyl acetate (4.05 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.10 g) were heated under reflux overnight in the presence of tetrakistriphenylphosphinepalladium(0) (0.16 g) in xylene in nitrogen atmosphere. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid, and the resulting aqueous layer was washed with ethyl acetate, adjusted to pH 10 with a 8N aqueous solution of sodium hydroxide, and then extracted with ethyl acetate. The extract was washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, to give a mixture (1.32 g) of 1-(4-ethylpiperazin-1-yl)-3-[4-(3-acetoxy-1,1-dimethylpropyl)phenyl]isoquinoline as a brown viscous oil and the starting material.

The resulting mixture (1.32 g) was then dissolved in methanol (30 ml), to which was then added a 5N aqueous solution of sodium hydroxide (3.00 ml), and the mixture was stirred at room temperature for 1.5 hr. The solvent was evaporated, and water was added to the resulting residue and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (toluene/acetone system), to give 0.74 g of the free compound of the title compound as a pale yellow

solid.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.40(s,6H), 2.01(t,J=7.4Hz,2H), 2.56(q,J=7.2Hz,2H), 2.76(br-t,4H), 3.55(t,J=7.2Hz,2H), 3.59(br-t,4H), 7.43-7.47(m,3H), 7.58(br-t,1H), 7.68(s,1H), 7.79(d,J=8.0Hz,1H), 8.07(d,J=8.0Hz,1H), 8.12(d,J=8.4Hz,2H).

The resulting free compound was converted into an oxalate in a conventional manner, and then recrystallized from ethanol/ether, to give the title compound as a pale brown powder.

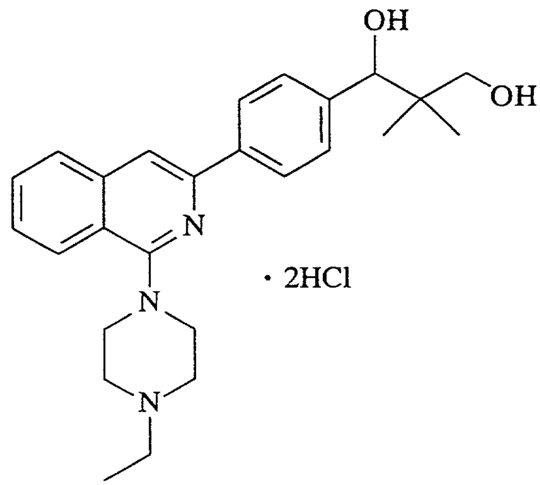
Oxalate:

m.p.; 134-135°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.26(t,J=7.2Hz,3H), 1.32(s,6H), 1.85(t,J=7.6Hz,2H), 3.12(br-q,2H), 3.23(d,J=7.6Hz,2H), 3.36(br-s,4H), 3.67(br-s,4H), 7.48(d,J=8.4Hz,2H), 7.60(br-t,1H), 7.73(br-t,1H), 7.98(d,J=8.0Hz,1H), 8.03(s,1H), 8.11(br-d,1H), 8.12(d,J=8.4Hz,2H).

MS(FAB) m/z 404$(M+H)^+$.

Example 391 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(1,3-dihydroxy-2,2-dimethylpropyl)phenyl]isoquinoline dihydrochloride



2,2,5,5-Tetramethyl-4-(4-tributylstannylphenyl)-1,3-dioxane (3.22 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.27 g) were heated under reflux overnight in the presence of tetrakistriphenylphosphinepalladium(0) (0.18 g) in xylene in nitrogen atmosphere. After cooling, the reaction solution was diluted with ethyl acetate and filtered. To the filtrate was added 2N hydrochloric acid. The resulting mixture was stirred at room temperature for 20 min. The resulting aqueous layer was washed with ethyl acetate, adjusted to pH 10 with a 8N aqueous solution of sodium hydroxide, and then extracted with ethyl acetate. The organic layer was washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (toluene/acetone system) and recrystallized from chloroform/n-hexane, to give 0.93 g of the free compound of the title compound as a pale brown powder.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.91(s,3H), 0.94(s,3H), 1.18(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.75(br-t,4H), 3.54-3.65(m,6H), 4.73(s,1H), 7.44(d,J=8.4Hz,2H), 7.46(br-t,1H), 7.59(br-t,1H), 7.69(s,1H), 7.79(d,J=8.4Hz,1H), 8.07(d,J=8.4Hz,1H), 8.15(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/ether, to give the title compound as a pale brown powder.

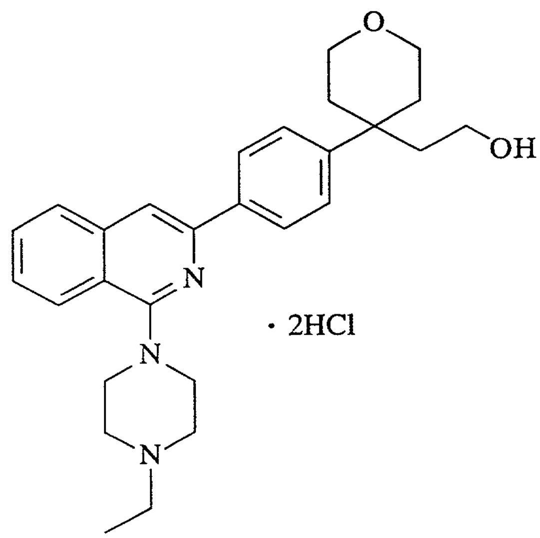
Hydrochloride:

m.p.; 150.5-151.5°C

^{1}H-NMR(400MHz,DMSO-d); δ (ppm) 0.70(s,3H), 0.84(s,3H), 1.33(t,J=7.2Hz,3H), 3.16(d,J=10.2Hz,1H), 3.21-3.27(m,2H), 3.34(d,J=10.2Hz,1H), 3.32-3.39(m,2H), 3.51(br-t,2H), 3.63(br-d,2H), 4.01(br-d,2H), 4.56(s,1H), 7.42(d,J=8.4Hz,2H), 7.60(br-t,1H), 7.74(br-t,1H), 7.99(d,J=8.0Hz,1H), 8.08(s,1H), 8.11(br-d,1H), 8.13(d,J=8.4Hz,2H), 10.79(br-s,1H).

MS(FAB) m/z 420$(M+H)^+$.

Example 392 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-{4-[4-(2-hydroxyethyl)tetrahydropyran-4-yl]phenyl}isoquinoline dihydrochloride



4-(2-Acetoxyethyl)-4-(4-tributylstannylphenyl)tetrahydropyran (2.20 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.83 g) were heated under reflux overnight in the presence of tetrakistriphenylphosphinepalladium(0) (0.12 g) in xylene in nitrogen atmosphere. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid, and the resulting aqueous layer was washed with ethyl acetate, adjusted to pH 10 with a 8N aqueous solution of sodium hydroxide, and then extracted with ethyl acetate. The extract was washed with a 10% sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, to give a mixture (1.14 g) of 1-(4-ethylpiperazin-1-yl)-3-{4-[4-(2-acetoxyethyl)tetrahydropyran-4-yl]phenyl}isoquinoline as a brown viscous oil and the starting material.

The resulting mixture (1.14 g) was subsequently dissolved

in methanol (30 ml), followed by the addition of a 5N aqueous solution of sodium hydroxide (2.35 ml), and the mixture was stirred at room temperature for 5 hr. The solvent was evaporated. To the resulting residue was added water, and the mixture was extracted with ethyl acetate. The extract was washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (toluene/acetone system), to give 0.83 g of the free compound of the title compound as a pale yellow solid.

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.92-1.99(m,2H), 1.98(t,J=7.2Hz,2H), 2.25(br-d,2H), 2.57(q,J=7.2Hz,2H), 2.77(br-t,4H), 3.46(t,J=7.2Hz,2H), 3.59-3.65(m,6H), 3.80-3.85(m,2H), 7.41(d,J=8.4Hz,2H), 7.47(br-t,1H), 7.60(br-t,1H), 7.70(s,1H), 7.80(d,J=8.0Hz,1H), 8.08(d,J=8.0Hz,1H), 8.17(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a pale brown powder.

Hydrochloride:

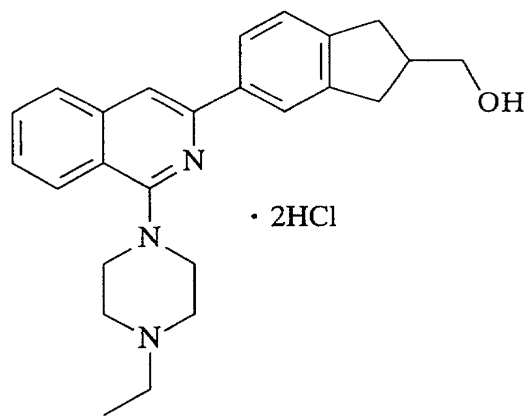
m.p.; 138-139°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 1.82-1.88(m,4H), 2.10(br-d,2H), 3.08-3.16(m,2H), 3.18-3.26(m,2H), 3.31-3.39(m,2H), 3.45(br-t,2H), 3.53-3.63(m,4H), 3.68-3.74(m,2H), 4.00(br-d,2H), 7.47(d,J=8.4Hz,2H), 7.61(br-t,1H),

7.75(br-t,1H), 8.00(d,J=8.0Hz,1H), 8.08(s,1H), 8.12(d,J=8.4Hz,1H), 8.17(d,J=8.4Hz,2H), 11.11(br-s,1H).

MS(FAB) m/z 446(M+H)$^+$.

Example 393 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(2-hydroxymethylindan-5-yl)isoquinoline dihydrochloride



2-Ethoxycarbonyl-5-(tributylstannyl)indane (3.04 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.87 g) were heated under reflux overnight in the presence of tetrakistriphenylphosphinepalladium(0) (0.12 g) in xylene in nitrogen atmosphere. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid, and the resulting aqueous layer was washed with ethyl acetate, adjusted to pH 10 with a 8N aqueous solution of sodium hydroxide, and then extracted with ethyl acetate. The extract was washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, to give 1-(4-ethylpiperazin-1-yl)-3-(2-ethoxycarbonylindan-5-yl)isoquinoline (1.06 g) as a brown viscous oil.

The resulting 1-(4-ethylpiperazin-1-yl)-3-(2-ethoxycarbonylindan-5-yl)isoquinoline (1.06 g) was dissolved in tetrahydrofuran (6 ml). Under cooling with a cooler of sodium chloride and ice, the solution was added to a suspension of lithium aluminum hydride (0.10 g) in tetrahydrofuran (10 ml), and the mixture was stirred for 20 min. To the resulting solution were sequentially added water (100 ml), a 5N aqueous solution of sodium hydroxide (100 ml) and water (300 ml), and the resulting precipitates were filtered off. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (toluene/acetone system), to give 0.35 g of the free compound of the title compound as a pale yellow amorphous.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.72-2.86(m,7H), 3.09-3.20(m,2H), 3.58(br-t,4H), 3.70(d,J=6.8Hz,2H), 7.29(d,J=8.0Hz,1H), 7.44(br-t,1H), 7.57(br-t,1H), 7.66(s,1H), 7.78(d,J=8.4Hz,1H), 7.95(br-d,1H), 8.01(s,1H), 8.07(d,J=8.4Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/IPE, to give the title compound as a pale brown powder.

Hydrochloride:

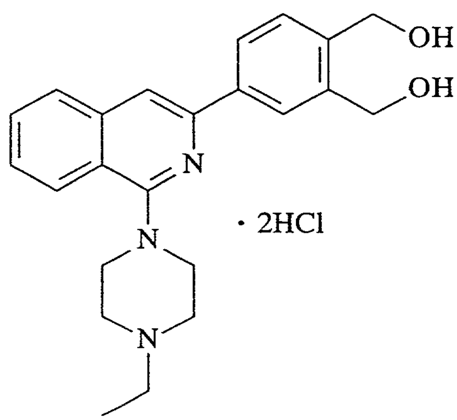
m.p.; 136.5-138°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 2.57-

2.65(m,1H), 2.70-2.80(m,2H), 2.96-3.07(m,2H), 3.21-3.27(m,2H), 3.31-3.40(m,2H), 3.41(d,J=6.8Hz,2H), 3.49(br-t,2H), 3.64(br-d,2H), 3.98(br-d,2H), 7.32(d,J=8.0Hz,2H), 7.59(br-t,1H), 7.73(br-t,1H), 7.97(d,J=8.0Hz,2H), 8.03(br-d,1H), 8.04(s,1H), 8.11(d,J=8.0Hz,1H), 10.79(br-s,1H).

MS(FAB) m/z 388$(M+H)^+$.

Example 394 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[(3,4-dihydroxymethyl)phenyl]isoquinoline dihydrochloride



3,4-Bis(acetoxymethyl)tributylstannylbenzene (1.91 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.00 g) were heated under reflux overnight in the presence of tetrakistriphenylphosphinepalladium(0) (0.14 g) in xylene in nitrogen atmosphere. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid, and the resulting aqueous layer was washed with ethyl acetate, adjusted to pH 10 with a 8N aqueous solution of sodium hydroxide, and then extracted with ethyl acetate. The extract was washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium

sulfate. The solvent was evaporated, to give a mixture (1.36 g) of 1-(4-ethylpiperazin-1-yl)-3-[3,4-bis(acetoxymethyl)phenyl]isoquinoline as a brown viscous oil and the starting material.

The resulting mixture (1.36 g) was then dissolved in methanol (30 ml), to which was then added a 5N aqueous solution of sodium hydroxide (7.22 ml), and the mixture was stirred at room temperature for 1 hr. The solvent was evaporated, and to the resulting residue was added water, and then the mixture was extracted with ethyl acetate. The extract was washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (toluene/acetone system), to give 0.79 g of the free compound of the title compound as a pale yellow solid.

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.76(br-t,4H), 3.58(br-t,4H), 4.81(s,2H), 4.87(s,2H), 7.46(d,J=7.6Hz,1H), 7.48(br-t,1H), 7.60(br-t,1H), 7.70(s,1H), 7.79(d,J=8.0Hz,1H), 8.07-8.11(m,2H), 8.17(d,J=1.6Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/IPE, to give the title compound as a pale brown powder.

Hydrochloride:

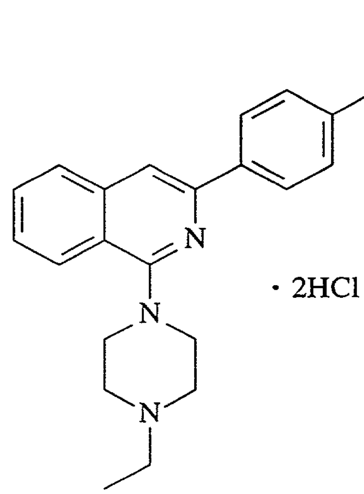
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 3.(m,2H),

3.32-3.40(m,2H), 3.54(br-t,2H), 3.64(br-d,2H), 3.99(br-d,2H), 4.61(s,2H), 4.64(s,2H), 7.53(d,J=8.2Hz,1H), 7.61(br-t,1H), 7.74(br-t,1H), 8.02(d,J=8.0Hz,1H), 8.07(s,1H), 8.08(dd,J=2.0,8.2Hz,1H), 8.12(d,J=8.8Hz,1H), 8.23(d,J=2.0Hz,1H), 11.11(br-s,1H).

MS(FAB) m/z 378$(M+H)^+$.

m.p.; 130.5-132°C (decomp.)

Example 395 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(1,4-dioxan-2-yl)phenyl]isoquinoline dihydrochloride



2-(4-Tributylstannylphenyl)-1,4-dioxane (2.63 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.15 g) were heated under reflux overnight in the presence of tetrakistriphenylphosphinepalladium(0) (0.16 g) in xylene in nitrogen atmosphere. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid, and the resulting aqueous layer was washed with ethyl acetate, adjusted to pH 10 with a 8N aqueous solution of sodium hydroxide, and then extracted with

ethyl acetate. The extract was washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.41 g of the free compound of the title compound as a pale brown viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.76(br-t,4H), 3.03(d,J=4.8Hz,2H), 3.59(br-t,4H), 3.84-3.90(m,2H), 3.93-3.99(m,2H), 5.12(t,J=4.8Hz,1H), 7.38(d,J=8.2Hz,2H), 7.45(br-t,1H), 7.58(br-t,1H), 7.67(s,1H), 7.78(d,J=8.0Hz,1H), 8.07(d,J=7.6Hz,1H), 8.11(d,J=8.2Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a yellow powder.

Hydrochloride:

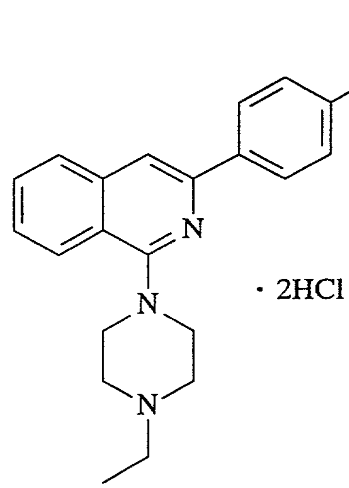
m.p.; 163-166°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 3.21-3.28(m,2H), 3.31-3.39(m,2H), 3.39(d,J=0.4Hz,2H), 3.50(br-t,2H), 3.63(br-d,2H), 3.76-3.92(m,4H), 4.01(br-d,2H), 5.03(t,J=0.4Hz,1H), 7.38-7.41(m,1H), 7.58-7.63(m,1H), 7.72-7.78(m,1H), 7.99(br-d,1H), 8.07-8.16(m,5H).

MS(FAB) m/z 404$(M+H)^+$.

Example 396 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-

(tetrahydrofuran-2-yl)phenyl]isoquinoline dihydrochloride



2-(4-Tributylstannylphenyl)tetrahydrofuran (1.88 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.18 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.17 g) in xylene in nitrogen atmosphere. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid, and the resulting aqueous layer was washed with ethyl acetate. Then, it was adjusted to pH 10 with a 8N aqueous solution of sodium hydroxide, extracted with ethyl acetate, washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.78 g of the free compound of the title compound as a pale yellow viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.81-

1.90(m,1H), 1.99-2.07(m,2H), 2.32-2.40(m,1H), 2.56(q,J=7.2Hz,2H), 2.76(br-t,4H), 3.59(br-t,4H), 3.97(dt,J=6.4,8.0Hz,1H), 4.14(dt,J=6.8,8.4Hz,1H), 4.97(t,J=7.0Hz,1H), 7.43(d,J=8.2Hz,2H), 7.45(br-t,1H), 7.58(br-t,1H), 7.69(s,1H), 7.79(d,J=8.4Hz,1H), 8.08(d,J=8.8Hz,1H), 8.14(d,J=8.2Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a yellow powder.

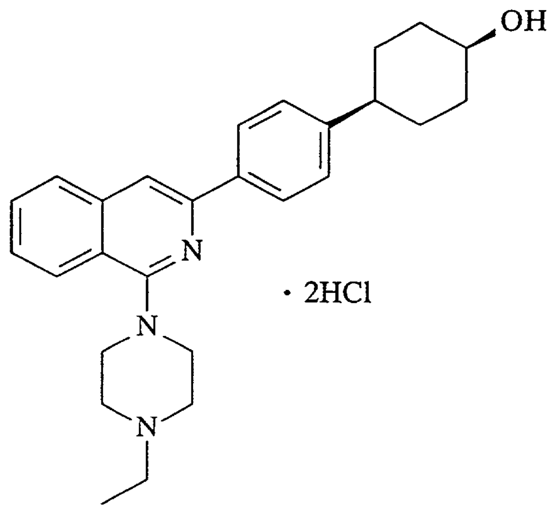
Hydrochloride:

m.p.; 129-130°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 1.66-1.75(m,1H), 1.93-2.01(m,2H), 2.30-2.38(m,1H), 3.20-3.27(m,2H), 3.31-3.39(m,2H), 3.52(br-t,2H), 3.63(br-d,2H), 3.81-3.87(m,1H), 3.98-4.05(m,3H), 4.87(t,J=7.2Hz,1H), 7.45(d,J=8.4Hz,2H), 7.61(br-t,1H), 7.75(br-t,1H), 7.99(d,J=8.4Hz,1H), 8.08(s,1H), 8.12(d,J=8.8Hz,1H), 8.16(d,J=8.4Hz,2H), 10.92(br-s,1H).

MS(FAB) m/z 388$(M+H)^+$.

Example 397 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(cis-4-hydroxycyclohexyl)phenyl]isoquinoline dihydrochloride



cis-4-(Tributylstannylphenyl)cyclohexyl acetate (1.37 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.11 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.16 g) in xylene in nitrogen atmosphere overnight. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid, and the resulting aqueous layer was washed with ethyl acetate. Then, it was adjusted to pH 10 with a 8N aqueous solution of sodium hydroxide, extracted with ethyl acetate, washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, to give a mixture (1.24 g) of 1-(4-ethylpiperazin-1-yl)-3-[4-(cis-4-acetoxycyclohexyl)phenyl]isoquinoline as a brown viscous oil and the starting material.

Then, the resulting mixture (1.24 g) was dissolved in methanol (20 ml). To the solution was added a 5N aqueous solution of sodium hydroxide (2.72 ml), and the mixture was

stirred at room temperature for 3.5 hr. The solvent was evaporated, and to the resulting residue was added water. The resulting mixture was extracted with ethyl acetate, washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (toluene/acetone system), to give 0.52 g of the free compound of the title compound as a pale brown amorphous.

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.17(br-t,4H), 1.94(br-t,4H), 2.56(q,J=7.2Hz,2H), 2.61(br-t,1H), 2.76(br-t,4H), 3.59(br-t,4H), 4.16(s,1H), 7.35(d,J=8.4Hz,2H), 7.45(br-t,1H), 7.58(br-t,1H), 7.67(s,1H), 7.78(d,J=8.0Hz,1H), 8.07(br-d,1H), 8.10(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/IPE, to give the title compound as a pale brown powder.

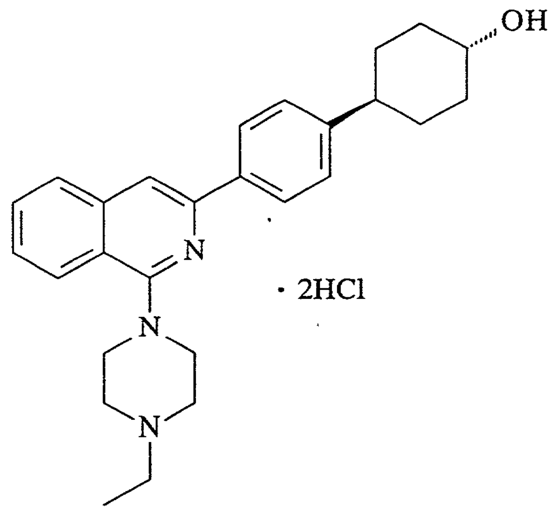
Hydrochloride:

m.p.; 152-153°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.32(t,J=7.2Hz,3H), 1.57(br-t,4H), 1.77(br-d,2H), 1.84-1.94(m,2H), 2.58(br-t,1H), 3.21-3.28(m,2H), 3.31-3.39(m,2H), 3.47(br-t,2H), 3.64(br-d,2H), 3.92(br-s,1H), 4.00(br-d,2H), 7.36(d,J=8.6Hz,2H), 7.60(br-t,1H), 7.74(br-t,1H), 7.98(br-d,1H), 8.05(s,1H), 8.11(d,J=8.6Hz,2H), 10.56(br-s,1H).

MS(FAB) m/z 416$(M+H)^+$.

Example 398 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(trans-4-hydroxycyclohexyl)phenyl]isoquinoline dihydrochloride



Trans-4-(tributylstannylphenyl)cyclohexyl acetate(0.56 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.46 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.06 g) in xylene in nitrogen atmosphere overnight. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid, and the resulting aqueous layer was washed with ethyl acetate. Then, it was adjusted to pH 10 by a 8N aqueous solution of sodium hydroxide, extracted with ethyl acetate, washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, to give a mixture (0.44 g) of 1-(4-ethylpiperazin-1-yl)-3-[4-(trans-4-acetoxycyclohexyl)phenyl]isoquinoline as a brown viscous oil and the starting material.

The resulting mixture (0.44 g) was then dissolved in methanol (8 ml), to which was then added a 5N aqueous solution of sodium hydroxide (987 ml), and the mixture was stirred at room temperature for 3 hr. The solvent was evaporated, and to the resulting residue was added water, and the mixture was extracted with ethyl acetate. The extract was washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (toluene/acetone system), to give 0.13 g of the free compound of the title compound as a pale brown amorphous.

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 1.40-1.50(m,2H), 1.53-1.63(m,2H), 1.97(br-d,2H), 2.12(br-d,2H), 2.52-2.59(m,1H), 2.55(q,J=7.2Hz,2H), 2.75(br-t,4H), 3.58(br-t,4H), 3.67-3.74(m,1H), 7.30(d,J=8.4Hz,2H), 7.44(br-t,1H), 7.57(br-t,1H), 7.66(s,1H), 7.77(d,J=8.0Hz,1H), 8.06-8.10(m,3H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/IPE, to give the title compound as a pale brown powder.

Hydrochloride:

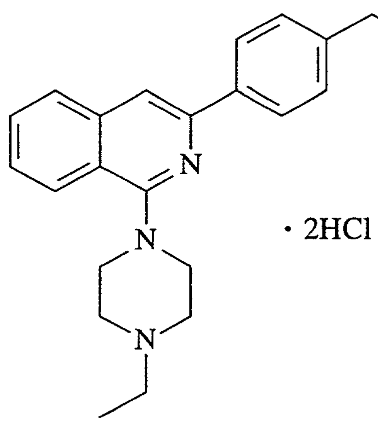
m.p.; 157-158°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.27-1.37(m,2H), 1.33(t,J=7.2Hz,3H), 1.47-1.58(m,2H), 1.82(br-d,2H), 1.95(br-d,2H), 3.20-3.27(m,2H), 3.31-3.38(m,2H), 3.46-

3.53(m,3H), 3.63(br-d,2H), 3.99(br-d,2H), 7.36(d,J=8.4Hz,2H), 7.60(br-t,1H), 7.74(br-t,1H), 7.98(d,J=8.0Hz,1H), 8.04(s,1H), 8.09-8.12(m,3H), 10.77(br-s,1H).

MS(FAB) m/z 416(M+H)$^+$.

Example 399 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(tetrahydropyran-4-yl)methylphenyl]isoquinoline dihydrochloride



4-(Tetrahydrofuran-4-yl)methyltributylstannylbenzene (0.67 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.59 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.08 g) in xylene in nitrogen atmosphere overnight. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted in 2N hydrochloric acid, and the resulting aqueous layer was washed with ethyl acetate. Then, it was adjusted to pH 10 with a 8N aqueous solution sodium hydroxide, extracted with ethyl acetate, washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the

resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.30 g of the free compound of the title compound as a pale yellow viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.32-1.43(m,2H), 1.61(br-d,2H), 1.75-1.86(m,1H), 2.56(q,J=7.2Hz,2H), 2.61(d,J=6.8Hz,2H), 2.76(br-t,4H), 3.35(br-t,2H), 3.59(br-t,4H), 3.96(br-q,2H), 7.24-7.26(m,2H), 7.45(br-t,1H), 7.58(br-t,1H), 7.68(s,1H), 7.79(d,J=8.0Hz,1H), 8.07-8.11(m,3H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with in ethanol/ether, to give the title compound as a yellow powder.

Hydrochloride:

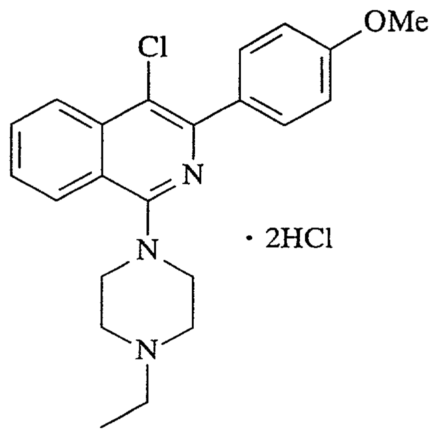
m.p.; 182-184°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.19-1.30(m,2H), 1.33(t,J=7.2Hz,3H), 1.51(br-d,2H), 1.72-1.84(m,1H), 2.58(d,J=7.2Hz,2H), 3.20-3.28(m,4H), 3.31-3.39(m,2H), 3.53(br-t,2H), 3.62(br-d,2H), 3.82(br-q,2H), 3.99(br-d,2H), 7.31(d,J=8.4Hz,2H), 7.60(br-t,1H), 7.74(br-t,1H), 7.98(d,J=7.6Hz,1H), 8.06(s,1H), 8.12(br-d,3H), 11.00(br-s,1H).

MS(FAB) m/z 416$(M+H)^+$.

Example 400 Synthesis of 4-chloro-1-(4-ethylpiperazin-1-

yl)-3-(4-methoxyphenyl)isoquinoline dihydrochloride



Phosphorus pentachloride (12.50 g) was added to 3-(4-methoxyphenyl)-1,2-dihydroisoquinolin-2-one (5.03 g) obtained in Example 10-1, and the mixture was stirred at 140°C overnight. Water was added to the reaction solution, and the mixture was extracted with ethyl acetate. The extract was washed sequentially with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (ethyl acetate/n-hexane system) and recrystallized from chloroform/n-hexane, to give 1,4-dichloro-3-(4-methoxyphenyl)isoquinoline (2.17 g).

To the resulting 1,4-dichloro-3-(4-methoxyphenyl)isoquinoline (0.30 g) were added potassium carbonate (0.14 g), N-ethylpiperazine (126 ml) and N,N-dimethylformamide (10 ml). The resulting mixture was stirred at room temperature overnight. To the mixture was then added N-ethylpiperazine (126 ml), and the mixture was stirred at room temperature for 4 hr. Still additionally, N-ethylpiperazine

(378 ml) was added thereto, and the mixture was stirred at 50°C for 1.5 hr. To the reaction solution was added water, and the mixture was extracted with ethyl acetate. The extract was washed sequentially with water (four times) and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (ethyl acetate/acetone system), to give 0.10 g of the free compound of the title compound as a colorless viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 2.54(q,J=7.2Hz,2H), 2.72(br-t,4H), 3.52(br-t,4H), 3.88(s,3H), 7.01(d,J=9.0Hz,2H), 7.53(br-t,1H), 7.72(br-t,1H), 7.88(d,J=9.0Hz,2H), 8.09(d,J=8.0Hz,1H), 8.27(d,J=8.0Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/IPE, to give the title compound as a yellow powder.

Hydrochloride:

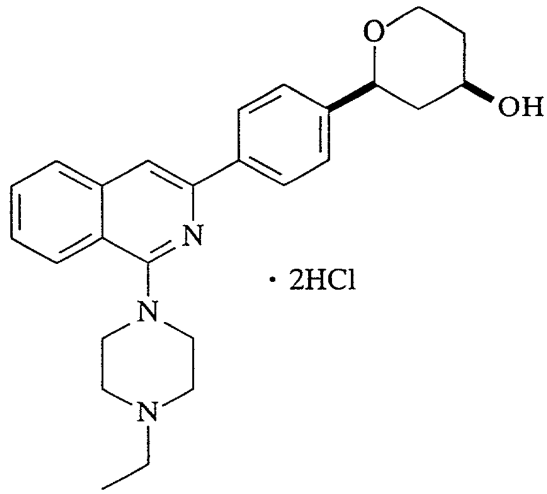
m.p.; 200.5-201.5°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.31(t,J=7.2Hz,3H), 3.18-3.25(m,2H), 3.28-3.36(m,2H), 3.50(br-t,2H), 3.58(br-d,2H), 3.84(s,3H), 3.95(br-d,2H), 7.08(d,J=9.0Hz,2H), 7.74(br-t,1H), 7.81(d,J=9.0Hz,2H), 7.93(br-t,1H), 8.20(d,J=8.0Hz,1H), 8.26(d,J=8.0Hz,1H), 10.95(br-s,1H).

MS(FAB) m/z 382, 384$(M+H)^+$.

<u>Example 401</u> <u>Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-</u>

(cis-4-hydroxytetrahydropyran-2-yl)phenyl]isoquinoline dihydrochloride



cis-4-Acetoxy-2-(tributylstannylphenyl)tetrahydrofuran (1.81 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.98 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.14 g) in xylene in nitrogen atmosphere overnight. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted in 2N hydrochloric acid, and the resulting aqueous layer was washed with ethyl acetate. Then, it was adjusted to pH 10 by a 8N aqueous solution of sodium hydroxide, extracted with ethyl acetate, washed with a 10% aqueous solution of sodium carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, to give a mixture of 1-(4-ethylpiperazin-1-yl)-3-[4-(cis-4-acetoxytetrahydropyran-2-yl)phenyl]isoquinoline as a brown viscous oil and the starting material.

Then, the resulting mixture was dissolved in methanol (20 ml). To the solution was added a 5N aqueous solution of sodium hydroxide (3.0 ml), and the mixture was stirred at room temperature overnight. The solvent was evaporated, and to the resulting residue was added water, and the mixture was then extracted with ethyl acetate. The extract was washed with brine and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.75 g of the free compound of the title compound as a pale brown amorphous.

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.55-1.72(m,2H), 1.97-2.03(m,1H), 2.21-2.27(m,1H), 2.56(q,J=7.2Hz,2H), 2.76(br-t,4H), 3.59-3.65(m,5H), 3.94-4.02(m,1H), 4.19-4.24(m,1H), 4.39(dd,J=2.0,11.4Hz,1H), 7.42-7.48(m,1H), 7.45(d,J=8.4Hz,2H), 7.58(br-t,1H), 7.69(s,1H), 7.79(d,J=8.0Hz,1H), 8.08(d,J=8.0Hz,1H), 8.15(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/IPE, to give the title compound as a yellow powder.

Hydrochloride:

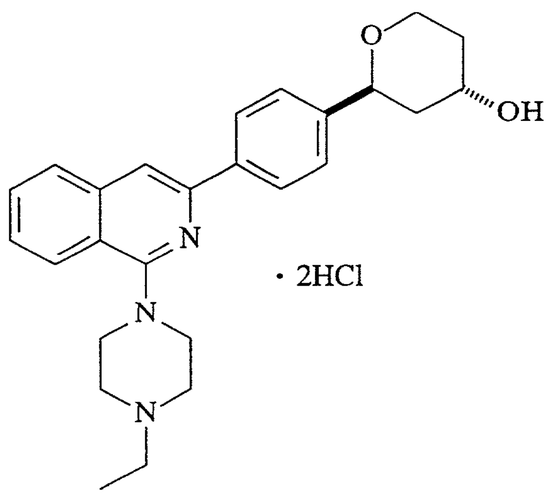
m.p.; 148-149.5°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.28-1.36(m,1H), 1.34(t,J=7.2Hz,3H), 1.39-1.49(m,1H), 1.81-1.86(m,1H), 2.06-2.11(m,1H), 3.20-3.26(m,2H), 3.31-3.39(m,2H), 3.48-

3.64(m,5H), 3.74-3.82(m,1H), 3.99(br-d,2H), 4.02-4.07(m,1H), 4.38(dd,J=1.6,11.2Hz,1H), 7.46(d,J=8.4Hz,2H), 7.61(br-t,1H), 7.75(br-t,1H), 7.99(d,J=8.4Hz,1H), 8.09(s,1H), 8.12(d,J=8.4Hz,1H), 8.16(d,J=8.4Hz,2H), 11.09(br-s,1H).

MS(FAB) m/z 418$(M+H)^+$.

Example 402 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(trans-4-hydroxytetrahydropyran-2-yl)phenyl]isoquinoline dihydrochloride



trans-4-Acetoxy-2-(tributylstannylphenyl)tetrahydropyran (3.35 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.36 g) were heated under reflux in the presence of tetrakistriphenylphosphinepalladium(0) (0.19 g) in xylene in nitrogen atmosphere overnight. After cooling, the reaction solution was diluted with ethyl acetate and filtered. The filtrate was extracted with 2N hydrochloric acid, and the resulting aqueous phase was washed with ethyl acetate. Then, it was adjusted to pH 10 by a 8N aqueous solution of sodium

hydroxide, extracted with ethyl acetate, washed with brine, and dried over magnesium sulfate. The solvent was evaporated, to give a mixture of 1-(4-ethylpiperazin-1-yl)-3-[4-(trans-4-acetoxytetrahydropyran-2-yl)phenyl]isoquinoline as a brown viscous oil and the starting material.

Then, the resulting mixture was dissolved in methanol (20 ml). To the solution was added a 5N aqueous solution of sodium hydroxide (3.0 ml), and the mixture was stirred at room temperature overnight. The solvent was evaporated, and to the residue was added water, and the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 1.06 g of the free compound of the title compound as a brown amorphous.

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.64-1.70(m,1H), 1.88-2.06(m,3H), 2.56(q,J=7.2Hz,2H), 2.76(br-t,4H), 3.59(br-t,4H), 3.95-4.00(m,1H), 4.07-4.13(m,1H), 4.34-4.37(m,1H), 4.89(dd,J=4.8,9.2Hz,1H), 7.45(br-t,1H), 7.46(d,J=8.4Hz,2H), 7.58(br-t,1H), 7.69(s,1H), 7.79(d,J=8.0Hz,1H), 8.07(d,J=8.4Hz,1H), 8.14(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/IPE, to give the title compound as a yellow powder.

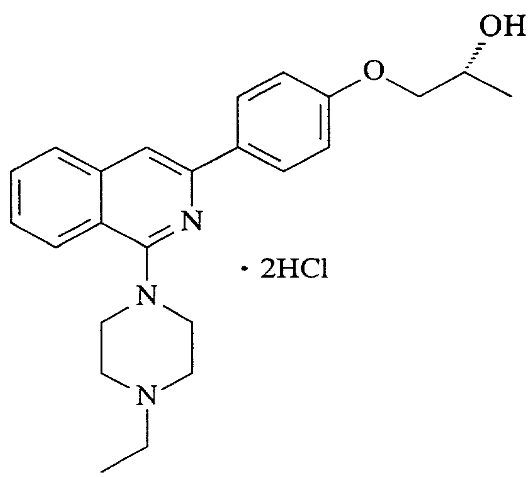
Hydrochloride:

m.p.; 151-152.5°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 1.55(br-d,1H), 1.68(br-t,1H), 1.75-1.86(m,2H), 3.19-3.26(m,2H), 3.31-3.39(m,2H), 3.53-3.64(m,4H), 3.82(dd,J=4.6,10.6Hz,1H), 3.92-4.00(m,4H), 4.79(dd,J=2.0,11.2Hz,1H), 7.44(d,J=8.2Hz,2H), 7.61(br-t,1H), 7.75(br-t,1H), 7.99(d,J=8.0Hz,1H), 8.08(s,1H), 8.12(d,J=8.4Hz,1H), 8.16(d,J=8.2Hz,2H), 11.29(br-s,1H).

MS(FAB) m/z 418(M+H)$^+$.

Example 403 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxypropoxy)phenyl]isoquinoline dihydrochloride



According to the method of Example 7, 1-(4-ethylpiperazin-1-yl)-3-(4-hydroxyphenyl)isoquinoline was obtained. In the same manner as in Example 287, subsequently, 1-(4-ethylpiperazin-1-yl)-3-{4-[2-(R)-(tert-butyldimethylsilyloxy)propoxy]phenyl}isoquinoline (0.43 g) was obtained.

To the resulting 1-(4-ethylpiperazin-1-yl)-3-{4-[2-(R)-(tert-butyldimethylsilyloxy)propoxy]phenyl}isoquinoline

(0.43 g) were added methanol (10 ml) and 2N hydrochloric acid (50 ml) and dissolved, and the resulting mixture was stirred at room temperature for 4.5 hr. The solvent was evaporated, and the resulting residue was adjusted to pH 10 by a 8N aqueous solution of sodium hydroxide, which was then extracted with ethyl acetate. The extract was washed with brine and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.22 g of the free compound of the title compound as a colorless amorphous.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.32(d,J=6.4Hz,3H), 2.56(q,J=7.2Hz,2H), 2.76(br-t,4H), 3.59(br-t,4H), 3.87(dd,J=8.0,9.2Hz,1H), 4.02(dd,J=2.8,8.2Hz,1H), 4.20-4.28(m,1H), 7.01(d,J=8.8Hz,2H), 7.44(br-t,1H), 7.57(br-t,1H), 7.62(s,1H), 7.77(d,J=8.0Hz,1H), 8.06(d,J=8.4Hz,1H), 8.12(d,J=8.8Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a yellow powder.

Hydrochloride:

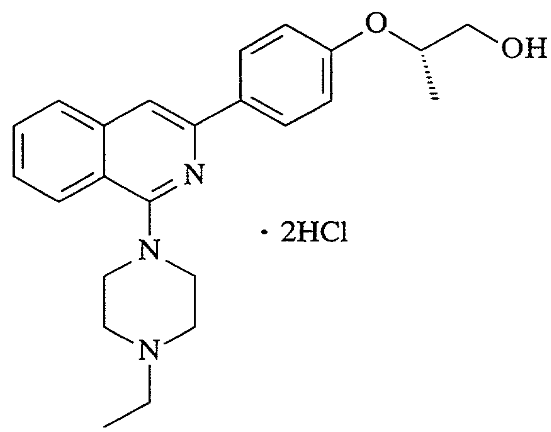
m.p.; 112-114°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.18(d,J=6.0Hz,3H), 1.33(t,J=7.2Hz,3H), 3.21-3.28(m,2H), 3.31-3.39(m,2H),

3.48(br-t,2H), 3.63(br-d,2H), 3.85-4.02(m,5H), 7.07(d,J=8.8Hz,2H), 7.58(br-t,1H), 7.72(br-t,1H), 7.96(d,J=8.4Hz,1H), 8.00(s,1H), 8.10(d,J=8.0Hz,1H), 8.15(d,J=8.8Hz,2H), 10.68(br-s,1H).

MS(FAB) m/z 392$(M+H)^+$.

Example 404 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxy-1-methylethoxy)phenyl]isoquinoline dihydrochloride



According to the method of Example 7, 1-(4-ethylpiperazin-1-yl)-3-(4-hydroxyphenyl)isoquinoline was obtained. In the same manner as in Example 287, subsequently, 1-(4-ethylpiperazin-1-yl)-3-{4-[2-trityloxy-1-(S)-methylethoxy)]phenyl}isoquinoline (1.21 g) in colorless viscous oil was prepared.

To the resulting 1-(4-ethylpiperazin-1-yl)-3-{4-[2-trityloxy-1-(S)-methylethoxy]phenyl}isoquinoline (1.21 g) were added benzene (10 ml), methanol (50 ml) and 2N hydrochloric acid (10 ml) and dissolved, and the resulting mixture was stirred at room temperature for 45 min. The solvent was evaporated, and the resulting residue was adjusted to pH 10 by

a 8N aqueous solution of sodium hydroxide, which was then extracted with ethyl acetate. The extract was washed with brine and dried over magnesium sulfate. The solvent was evaporated, to give 0.36 g of the free compound of the title compound as a colorless amorphous.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 1.32(d,J=6.0Hz,3H), 2.56(q,J=7.2Hz,2H), 2.76(br-t,4H), 3.59(br-t,4H), 3.75(dd,J=6.4,11.6Hz,1H), 3.80(dd,J=3.6,11.6Hz,1H), 4.55-4.62(m,1H), 7.03(d,J=8.8Hz,2H), 7.44(br-t,1H), 7.57(br-t,1H), 7.62(s,1H), 7.77(d,J=8.0Hz,1H), 8.06(d,J=7.2Hz,1H), 8.12(d,J=8.8Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a yellow powder.

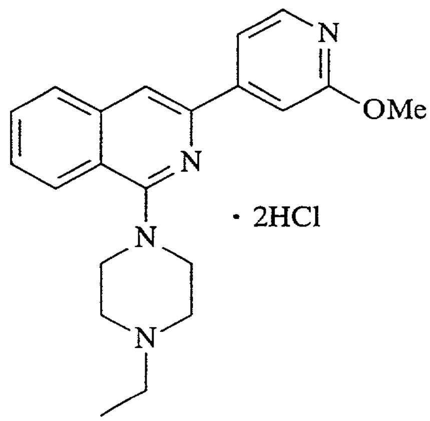
Hydrochloride:

m.p.; 128-129°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.25(d,J=6.0Hz,3H), 1.33(t,J=7.2Hz,3H), 3.20-3.26(m,2H), 3.31-3.38(m,2H), 3.48-3.63(m,6H), 4.48-4.56(m,1H), 7.07(d,J=9.0Hz,2H), 7.57(br-t,1H), 7.72(br-t,1H), 7.95(d,J=8.0Hz,1H), 7.99(s,1H), 8.10(d,J=8.4Hz,1H), 8.13(d,J=9.0Hz,2H), 11.03(br-s,1H).

MS(FAB) m/z 392$(M+H)^+$.

Example 405 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(2-methoxypyridin-4-yl)isoquinoline



To 3-(2-methoxypyridin-4-yl)isoquinolin-1-one (1.22 g) obtained by reacting N-methyl-o-toluamide (2.90 g) and 4-cyano-2-methoxypyridine (2.60 g) according to the method of Example 10-1 was added phosphorus oxychloride (25.7 g), and the resulting mixture was heated at 100°C for 2 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and purified water. The ethyl acetate layer was washed with water, an aqueous solution of saturated sodium bicarbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting 1-chloro-3-(2-methoxyphenyl)isoquinoline was reacted as it was with N-ethylpiperazine (20 ml) at 120°C for 8 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and purified water. The ethyl acetate layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to the free compound of the title compound as a pale yellow oil (0.62 g, yield; 9.2%).

The resulting free compound was converted into a hydrochloride in a conventional manner, to give a yellow powder.

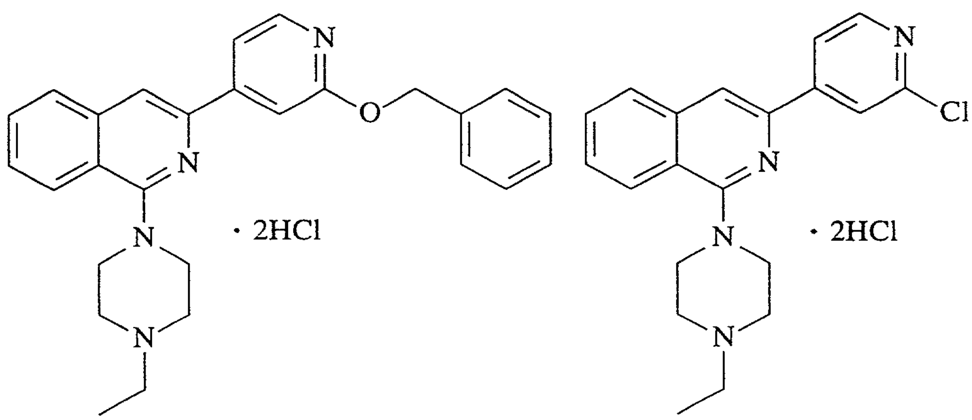
Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.32(t,J=7.2Hz,3H), 3.18-3.28(m,2H), 3.28-3.41(m,2H), 3.48-3.67(m,4H), 3.94(s,3H), 3.99-4.08(m,2H), 7.62(br-s,1H), 7.66-7.73(m,1H), 7.77-7.84(m,2H), 8.04(br-d,1H), 8.16(br-d,1H), 8.28-8.33(m,2H), 10.98(m,1H).

m.p.; 174-176°C

MS(FAB) m/z 349(M+H)$^+$.

Example 406 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(2-benzyloxypyridin-4-yl)isoquinoline and 1-(4-ethylpiperazin-1-yl)-3-(2-chloropyridin-4-yl)isoquinoline



To 3-(2-benzyloxypyridin-4-yl)isoquinolin-1-one (2.84 g) obtained by reacting N-methyl-o-toluamide (3.00 g) and 4-cyano-2-benzyloxypyridine (4.20 g) according to the method of Example 10-1 was added phosphorus oxychloride (37.7 g), and the resulting mixture was heated at 100°C for 2 hr. The reaction solution was evaporated, and to the resulting residue were added

ethyl acetate and purified water. The ethyl acetate layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting 1-chloro-3-(2-benzyloxypyridin-4-yl)isoquinoline was reacted as it was with N-ethylpiperazine (20 ml) at 120°C for 8 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and purified water. The ethyl acetate layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 1-(4-ethylpiperazin-1-yl)-3-(2-benzyloxypyridin-4-yl)isoquinoline (0.21 g) and 1-(4-ethylpiperazin-1-yl)-3-(2-chloropyridin-4-yl)isoquinoline (0.32 g), as pale yellow oils.

These resulting compounds were individually converted into hydrochlorides in conventional methods, to give a yellow amorphous and a yellow powder.

1-(4-Ethylpiperazin-1-yl)-3-(2-benzyloxypyridin-4-yl)isoquinoline hydrochloride (yellow amorphous):

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.32(t,J=7.2Hz,3H), 3.18-3.40(m,4H), 3.41-3.53(m,2H), 3.58-3.66(m,2H), 3.96-4.07(m,2H), 5.42(s,2H).

MS(FAB) m/z 425$(M+H)^+$.

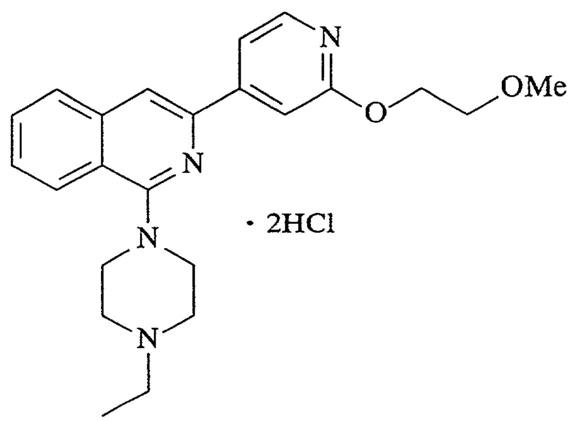
1-(4-Ethylpiperazin-1-yl)-3-(2-chloropyridin-4-yl)isoquinoline hydrochloride (yellow powder):

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.32(t,J=7.2Hz,3H), 3.18-

3.41(m,4H), 3.44-3.56(m,2H), 3.58-3.66(m,2H), 4.00-4.08(m,2H), 7.68-7.75(m,1H), 7.79-7.85(m,1H), 8.05(br-d,1H), 8.15-8.21(m,2H), 8.24(s,1H), 8.42(s,1H), 8.55(d,J=5.6Hz,1H).

m.p.; 165-167°C

Example 407 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[2-(2-methoxyethoxy)pyridin-4-yl]isoquinoline



60% oily sodium hydride (0.20 g) was added gradually to 2-methoxyethanol (50 ml), under ice-cooling. To the resulting solution was added 1-(4-ethylpiperazin-1-yl)-3-(2-chloropyridin-4-yl)isoquinoline (0.20 g) obtained in the previous Example, and the mixture was heated under reflux for 3 days. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and purified water. The ethyl acetate layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the title compound (0.12 g) as a pale yellow oil.

The resulting compound was converted into a hydrochloride

in a conventional manner, to give a yellow powder.

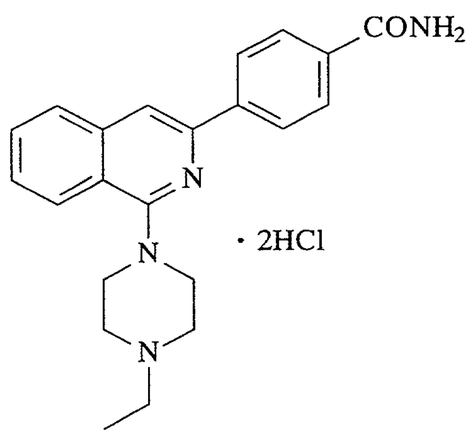
Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 3.17-3.27(m,2H), 3.27-3.41(m,2H), 3.50-3.67(m,4H), 3.69-3.74(m,2H), 3.97-4.07(m,2H), 4.44-4.49(m,2H), 7.64(br-s,1H), 7.66-7.75(m,1H), 7.76-7.85(m,1H), 8.01-8.06(m,1H), 8.14-8.20(m,1H), 8.29(d,J=5.6Hz,1H), 8.34(s,1H), 11.52(m,1H).

m.p.; 139-140°C

MS(FAB) m/z 393$(M+H)^+$.

Example 408 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(4-carbamoylphenyl)isoquinoline



1-(4-Ethylpiperazin-1-yl)-3-(4-cyanophenyl)isoquinoline (1.0 g) obtained in Example 62 was reacted in concentrated sulfuric acid (40 ml) at 60°C for 5 hr. The reaction solution was cooled and then poured over ice, and was then adjusted to pH 8 to 9 by a 8N aqueous solution of sodium hydroxide. The resulting white precipitates were collected by filtration, washed with water and dried, to give the title compound (0.25 g, yield; 23.8%).

The resulting compound was converted into a hydrochloric in a conventional manner, to give a yellow powder (0.21 g).

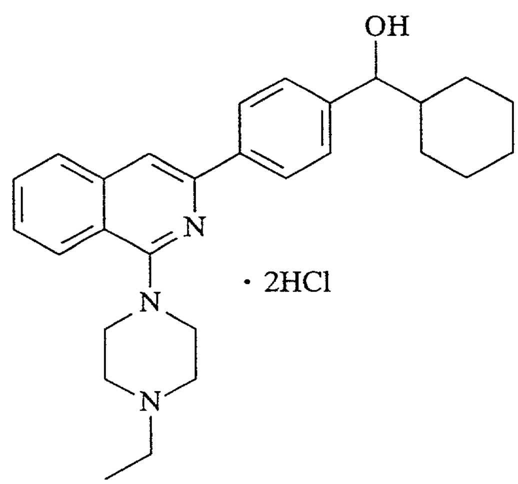
Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 3.18-3.28(m,2H), 3.30-3.41(m,2H), 3.51-3.67(m,4H), 3.98-4.06(m,2H), 7.43(m,1H), 7.62-7.67(m,1H), 7.75-7.80(m,1H), 8.02(d,J=8.4Hz,2H), 8.05-8.12(m,1H), 8.14(d,J=8.4Hz,1H), 8.21(s,1H), 8.28(d,J=8.4Hz,2H), 11.14(m,1H).

m.p.; 197-199°C

MS(FAB) m/z 361(M+H)$^+$.

Example 409 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(cyclohexylhydroxymethyl)phenyl]isoquinoline



To a solution of 1-(4-ethylpiperazin-1-yl)-3-(4-formylphenyl)isoquinoline (0.35 g) obtained as an intermediate product in Example 17, in tetrahydrofuran (5 ml) was added 2M cyclohexylmagnesium chloride/ether solution (1 ml) at room temperature, and the mixture was reacted for 0.5 hr. The reaction solution was diluted with ethyl acetate, washed

sequentially with an aqueous solution of saturated ammonium chloride, water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the title compound (0.21 g) as a pale yellow oil.

The resulting compound was converted into a hydrochloride in a conventional manner, to give a yellow powder (0.18 g).

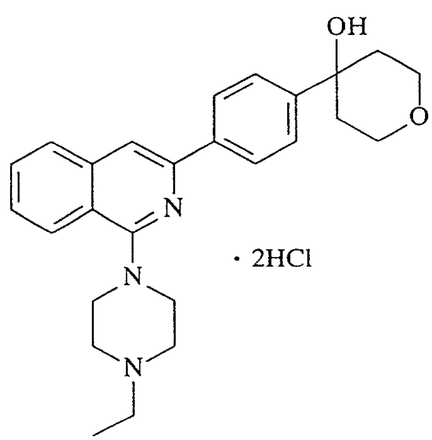
Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.34(t,J=7.2Hz,3H), 0.90-1.90(m,11H), 3.17-3.28(m,2H), 3.29-3.41(m,2H), 3.50-3.66(m,4H), 3.96-4.05(m,2H), 4.32(d,J=6.4Hz,1H), 7.40(d,J=8.4Hz,2H), 7.58-7.64(m,1H), 7.72-7.77(m,1H), 7.99(d,J=8.4Hz,1H), 8.07(s,1H), 8.10-8.16(m,3H), 11.28(m,1H).

m.p.; 153-155°C

MS(FAB) m/z 430(M+H)$^+$.

<u>Example 410 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(4-hydroxytetrahydropyran-4-yl)phenyl]isoquinoline</u>



To 3-(4-bromophenyl)isoquinolin-1-one (3.86 g) obtained by reacting N-methyl-o-toluamide (7.50 g) and 4-bromobenzonitrile (9.10 g) according to the method of Example 10-1 was added phosphorus oxychloride (38.6 g), and the resulting mixture was heated at 100°C for 2 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and purified water. The ethyl acetate layer was washed with water, an aqueous solution of saturated sodium bicarbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting 1-chloro-3-(4-bromophenyl)isoquinoline was reacted as it was with N-ethylpiperazine (30 ml) at 120°C for 8 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and purified water. The ethyl acetate layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 3-(4-bromophenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline (1.62 g) as a pale yellow oil.

A solution of the resulting 3-(4-bromophenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline (0.61 g) in tetrahydrofuran (30 ml) was cooled to -78°C, followed by the dropwise addition of 1.6M n-BuLi (1.1 ml) in nitrogen atmosphere. Fifteen minutes later, a solution of tetrahydropyran-4-one (0.17 g) in tetrahydrofuran (1 ml) was added thereto, and the temperature of the reaction mixture was gradually raised to room temperature.

Three hours later, an aqueous solution of saturated ammonium chloride was added thereto, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the title compound as a pale yellow oil (0.21 g, yield; 32.1%).

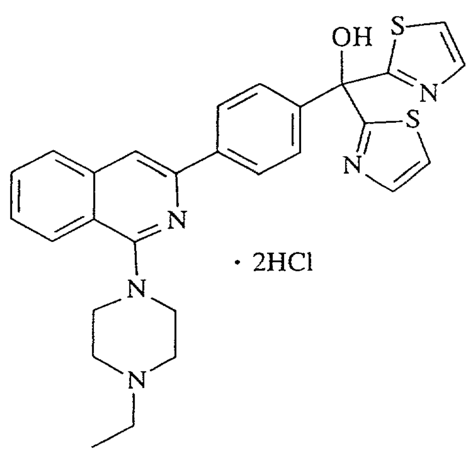
The resulting compound was converted into a hydrochloride in a conventional manner, to give a yellow amorphous.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 1.76(br-d,2H), 2.20-2.30(m,2H), 2.55(q,J=7.2Hz,2H), 2.76(m,4H), 3.58(m,4H), 3.89-4.02(m,4H), 7.43-7.48(m,1H), 7.56-7.62(m,1H), 7.59(d,J=8.4Hz,2H), 7.68(s,1H), 7.77(d,J=8.0Hz,1H), 8.08(d,J=8.0Hz,1H), 8.16(d,J=8.4Hz,2H).

MS(FAB) m/z 418(M+H)$^+$.

Example 411 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-{4-[bis(1,3-thiazol-2-yl)hydroxymethyl]phenyl}isoquinoline



A solution of thiazole (0.75 g) in tetrahydrofuran (40 ml) was cooled to -78 °C, followed by the dropwise addition of 2.5M n-BuLi (3.8 ml). Fifteen minutes later, a solution of 1-(4-ethylpiperazin-1-yl)-3-(4-formylphenyl)isoquinoline (1.0 g) obtained as an intermediate in Example 17, in tetrahydrofuran (20 ml) was added dropwise thereto. The temperature of the reaction solution was gradually raised to room temperature. The reaction solution was diluted with ethyl acetate, washed with an aqueous solution of saturated ammonium chloride, water and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the title compound (0.27 g) as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 2.55(d,J=7.2Hz,2H), 2.74(m,4H), 3.57(m,4H), 5.75(br-s,1H), 7.37(d,J=3.2Hz,2H), 7.45(br-t,1H), 7.56(br-t,1H), 7.65(s,1H), 7.73-7.80(m,3H), 7.82(d,J=3.2Hz,2H), 8.05(d,J=8.0Hz,1H), 8.14(d,J=8.0Hz,2H).

The resulting compound was converted into a hydrochloride in a conventional manner, to give a yellow powder (0.18 g).

Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.37(t,J=7.2Hz,3H), 3.17-3.62(m,8H), 3.96-4.03(m,2H), 7.70-7.76(m,5H), 7.80(d,J=3.2Hz,2H), 7.96(br-d,1H), 8.05(s,1H), 8.09(br-d,1H),

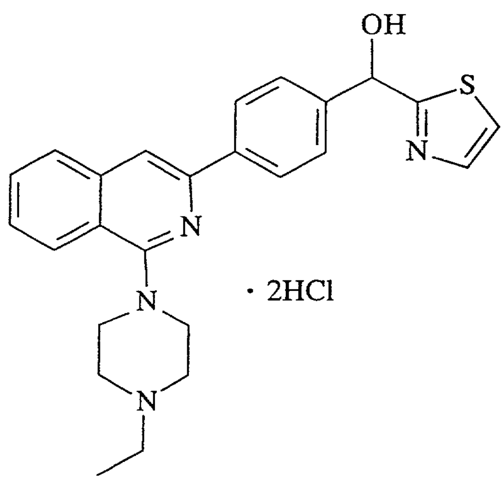
8.14(d,J=8.0Hz,2H).

m.p.; 157-158°C

MS(FAB) m/z 514(M+H)$^+$.

As a by-product, 1-(4-ethylpiperazin-1-yl)-3-[4-(1,3-thiazol-2-yl)carbonylphenyl]isoquinoline (0.18 g) was obtained.

Example 412 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(1,3-thiazol-2-yl)hydroxymethylphenyl]isoquinoline



1-(4-Ethylpiperazin-1-yl)-3-[4-(1,3-thiazol-2-yl)carbonylphenyl]isoquinoline (0.18 g) was dissolved in methanol (10 ml) and was reacted with sodium borohydride (0.02 g). The reaction solution was concentrated. The resulting residue was partitioned between ethyl acetate (50 ml) and water (20 ml). The ethyl acetate layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the title compound (0.12 g) as a pale yellow oil.

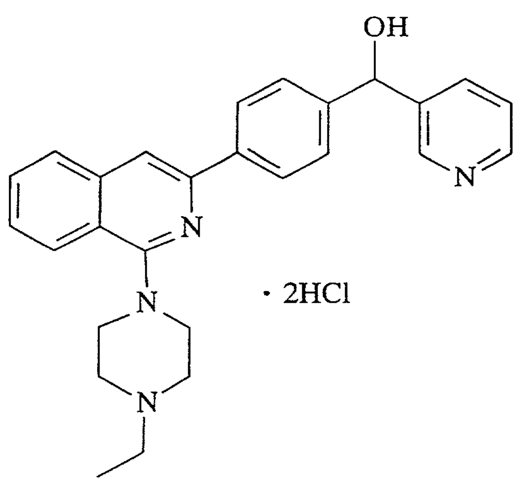
Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.58(d,J=7.2Hz,2H), 2.77(m,4H), 3.60(m,4H), 6.15(s,1H), 7.29(br-s,1H), 7.44(t,J=8.0Hz,1H), 7.55-7.60(m,1H), 7.58(d,J=8.0Hz,2H), 7.66(s,1H), 7.72(d,J=2.8Hz,2H), 7.77(d,J=8.0Hz,1H), 8.04(d,J=8.0Hz,1H), 8.16(d,J=8.0Hz,2H).

MS(FAB) m/z 431$(M+H)^+$.

The resulting compound was converted into a hydrochloride in a conventional manner, to give a yellow powder (0.10 g).

Example 413 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[(3-pyridyl)hydroxymethyl]isoquinoline



A solution of 1-(4-ethylpiperazin-1-yl)-3-bromoisoquinoline (0.39 g) obtained in Example 28-2, in tetrahydrofuran (10 ml) was cooled to -78°C, followed by the dropwise addition of 2.5M n-BuLi (0.6 ml). Fifteen minutes later, a solution of 3-formylpyridine (0.2 g) in tetrahydrofuran (3 ml) was added dropwise thereto. The temperature of the reaction solution was gradually raised to

room temperature. The reaction solution was diluted with ethyl acetate, washed with brine, water and an aqueous solution of saturated sodium chloride, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the title compound (0.15 g) as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.57(d,J=7.2Hz,2H), 2.74(m,4H), 3.55(m,4H), 5.80(s,1H), 7.00(s,1H), 7.23-7.28(m,1H), 7.46(br-t,1H), 7.57(br-t,1H), 7.65(br-d,1H), 7.75(br-d,1H), 8.04(br-d,2H), 8.52(br-d,1H), 8.72(s,1H).

The resulting compound was converted into an oxalate in a conventional manner, to give a pale yellow powder (0.17 g).

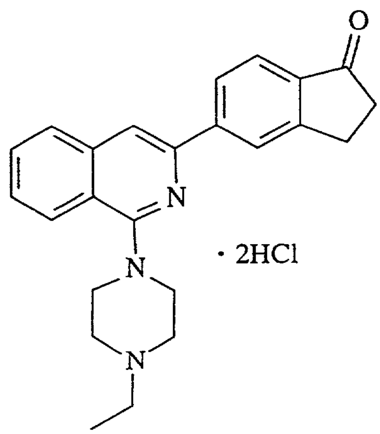
Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.25(t,J=7.2Hz,3H), 3.14(q,J=7.2Hz,2H), 3.21-3.70(m,8H), 7.33(dd,J=8.0,1.2Hz,1H), 7.58(t,J=7.6Hz,1H), 7.68(s,1H), 7.72(t,J=7.6Hz,1H), 7.83(d,J=7.6Hz,1H), 7.95(d,J=8.0Hz,1H), 7.95(d,J=8.0Hz,1H), 8.43(dd,J=4.8,1.6Hz,1H), 8.71(d,J=1.6Hz,1H).

m.p.; 174-175°C

MS(FAB) m/z 349$(M+H)^+$.

Example 414 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(1-indanon-5-yl)isoquinoline



5-Bromo-1-indanone (3.0 g) and hexabutylditin (8.2 g) were reacted in the presence of tetrakistriphenylphosphinepalladium(0) (0.3 g) in xylene (50 ml) at 140°C for 2 hr. After the reaction solution was back to room temperature, it was directly subjected to and purified by silica gel column chromatography (ethyl acetate/hexane system), to give 5-tributylstannyl-1-indanone (1.20 g) as a pale yellow oil. The resulting compound was subsequently reacted with 1-(4-ethylpiperazin-1-yl)-3-bromoisoquinoline (0.6 g) in the presence of tetrakistriphenylphosphinepalladium(0) (0.3 g) in xylene (50 ml) at 140°C for 4 hr. The reaction solution was extracted with a 2N aqueous solution of hydrochloric acid (20 ml), again basified with sodium carbonate, and then extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the title compound (0.41 g) as a pale yellow

oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.56(d,J=7.2Hz,2H), 2.73-2.81(m,6H), 3.20-3.26(m,2H), 3.60(m,4H), 7.50(t,J=7.6Hz,1H), 7.62(t,J=7.6Hz,1H), 7.79(s,1H), 7.81-7.86(m,2H), 8.09(br-d,1H), 8.15(br-d,1H), 8.29(s,1H).

The titled compound (0.21 g) was converted into a hydrochloride in a conventional manner, to give a yellow powder (0.19 g).

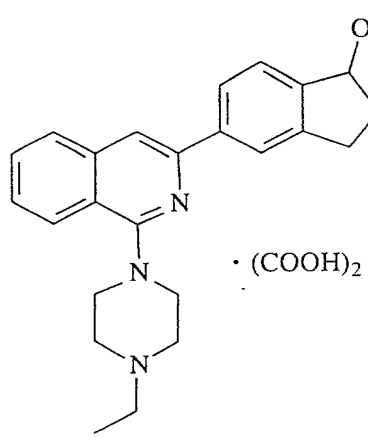
Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.32(t,J=7.2Hz,3H), 2.68-2.74(m,2H), 3.19-3.52(m,6H), 3.63(br-d,2H), 4.02(br-d,2H), 7.68(br-t,1H), 7.75-7.83(m,2H), 8.04(d,J=8.0Hz,1H), 8.16(d,J=8.0Hz,1H), 8.26-8.30(m,1H), 8.29(s,1H), 8.40(s,1H).

m.p.; 233°C (decomp.)

MS(FAB) m/z 372$(M+H)^+$.

Example 415 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(1-hydroxyindan-5-yl)isoquinoline



1-(4-Ethylpiperazin-1-yl)-3-(1-indanon-5-yl)isoquinoline (0.20 g) obtained in the previous Example was dissolved in methanol (20 ml), followed by the addition of sodium borohydride (0.10 g) at room temperature, and the mixture was reacted for 15 min. The reaction solution was concentrated, and the resulting residue was partitioned between ethyl acetate and water. The ethyl acetate layer was separated, washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the title compound (0.12 g) as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 1.96-2.07(m,1H), 2.50-2.60(m,3H), 2.75(m,4H), 2.86-2.96(m,1H), 3.10-3.21(m,1H), 3.58(m,4H), 5.29-5.33(m,1H), 7.46(br-t,1H), 7.51(d,J=8.0Hz,1H), 7.58(br-t,1H), 7.67(s,1H), 7.77(d,J=8.0Hz,1H), 8.03-8.09(m,2H), 8.05(s,1H).

The title compound was converted into an oxalate in a conventional manner, to give a pale yellow powder (0.11 g).

Oxalate:

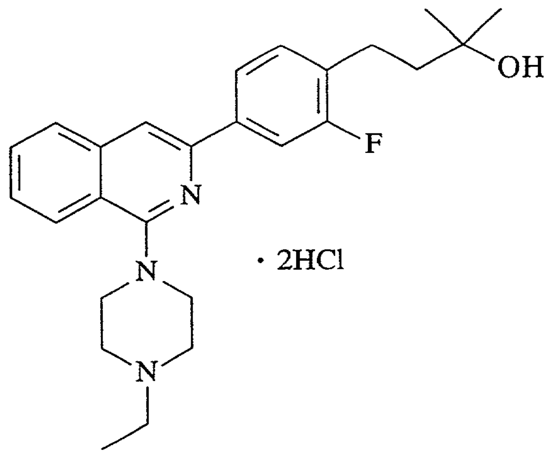
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.25(t,J=7.2Hz,3H), 1.78-1.88(m,1H), 2.35-2.43(m,1H), 2.75-2.86(m,1H), 2.94-3.08(m,1H), 3.09-3.70(m,10H), 5.10(br-t,1H), 7.45(d,J=8.4Hz,1H), 7.60(br-t,1H), 7.73(br-t,1H), 7.97(d,J=8.4Hz,1H), 8.04(s,1H), 8.05(s,1H),

8.11(d,J=8.8Hz,1H).

m.p.; 193-195°C

MS(FAB) m/z 374$(M+H)^+$.

Example 416 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxy-3-methylbutyl)-3-fluorophenyl]isoquinoline



To a suspension of 60% oily sodium hydride (0.18 g) in tetrahydrofuran (25 ml) was added triethylphosphonoacetate ester (1.0 g), under ice-cooling. After the evolution of the hydrogen was ceased, a solution of 1-(4-ethylpiperazin-1-yl)-3-(3-fluoro-4-formylphenyl)isoquinoline (0.65 g) obtained in Example 28-3 in tetrahydrofuran (10 ml) was added dropwise to the resulting reaction solution. After stirring for 2 hr, purified water was added to the reaction solution, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine, and dried over magnesium sulfate. The solvent was removed, and the resulting residue was dissolved in ethanol (10 ml), followed by the hydrogenation in the presence of platinum oxide (0.05 g). After

the catalyst was filtered off and washed with ethanol, the resulting filtrate was concentrated. To a solution of the resulting residue in tetrahydrofuran (10 ml) was added 3M methylmagnesium bromide/ether solution (1 ml), and the mixture was reacted at room temperature for 1 hr. An aqueous solution of ammonium chloride was added to the reaction solution, and then the mixture was extracted with ethyl acetate. The resulting ethyl acetate layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.28 g of the title compound as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 1.31(s,6H), 1.77-1.85(m,2H), 2.55(q,J=7.2Hz,3H), 2.73-2.81(m,6H), 3.57(m,4H), 7.27(t,J=8.0Hz,1H), 7.45(br-t,1H), 7.58(br-t,1H), 7.65(s,1H), 7.77(d,J=8.4Hz,1H), 7.82-7.79(m,2H), 8.06(d,J=8.0Hz,1H).

The resulting title compound was converted into a hydrochloride in a conventional manner, to give a pale yellow powder (0.20 g).

Hydrochloride:

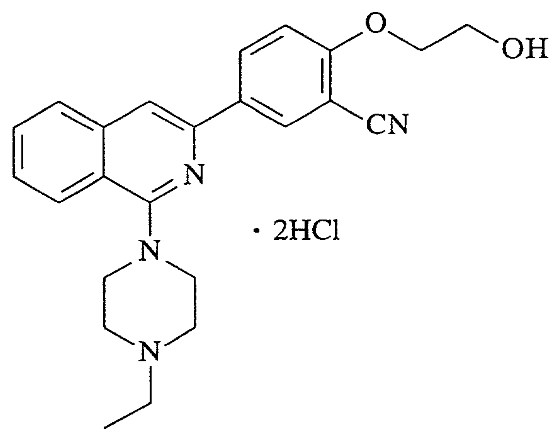
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.18(s,6H), 1.33(t,J=7.2Hz,3H), 1.62-1.69(m,2H), 2.66-2.75(m,2H), 3.18-3.29(m,2H), 3.36(br-q,2H), 3.51(br-t,2H), 3.63(br-d,2H), 4.00(br-d,2H), 7.41(t,J=8.0Hz,1H), 7.63(br-t,1H), 7.76(br-t,1H), 7.91-

8.00(m,3H), 8.10-8.15(m,2H), 10.86(m,1H).

m.p.; 206-207°C

MS(FAB) m/z 422(M+H)$^+$.

Example 417 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[3-cyano-4-(2-hydroxyethoxy)phenyl]isoquinoline



2-(2-Benzyloxyethoxy)-5-bromobenzonitrile (2.01 g) and hexabutylditin (3.84 g) were reacted in xylene (50 ml) in the presence of tetrakistriphenylphosphinepalladium(0) (0.20 g) at 140°C for 1.5 hr. After the reaction solution was back to room temperature, it was directly subjected to silica gel column chromatography (ethyl acetate/hexane system), to give 2-(2-benzyloxyethoxy)-5-tributylstannylbenzonitrile (1.70 g) as a pale yellow oil. Further, the resulting compound was reacted as it was with 1-(4-ethylpiperazin-1-yl)-3-bromoisoquinoline (0.48 g) in xylene (50 ml) in the presence of tetrakistriphenylphosphinepalladium(0) (0.21 g) at 140°C for 4 hr. The reaction solution was extracted with a 2N aqueous solution of hydrochloric acid (20 ml) and basified again with sodium carbonate, and then extracted with ethyl acetate. The

ethyl acetate layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 1-(4-ethylpiperazin-1-yl)-3-[3-cyano-4-(2-benzyloxyethoxy)phenyl]isoquinoline (0.52 g) as a pale yellow oil.

1-(4-Ethylpiperazin-1-yl)-3-[3-cyano-4-(2-benzyloxyethoxy)phenyl]isoquinoline (0.50 g) was dissolved in methanol (20 ml), followed by the hydrogenation in the presence of 10% palladium/carbon catalyst (0.05 g) at room temperature. After the catalyst was filtered off and washed with methanol, the resulting filtrate was concentrated, to give 0.28 g of the title compound as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,3H), 2.77(m,4H), 3.58(m,4H), 4.05(m,3H), 4.24(m,3H), 7.08(d,J=8.0Hz,1H), 7.47(br-t,1H), 7.60(s,1H), 7.58-7.63(m,1H), 7.78(d,J=8.0Hz,1H), 8.06(d,J=8.0Hz,1H), 8.35(d,J=8.0Hz,1H), 8.39(s,1H).

The resulting title compound was converted into a hydrochloride in a conventional manner, to give a yellow powder (0.25 g).

Hydrochloride:

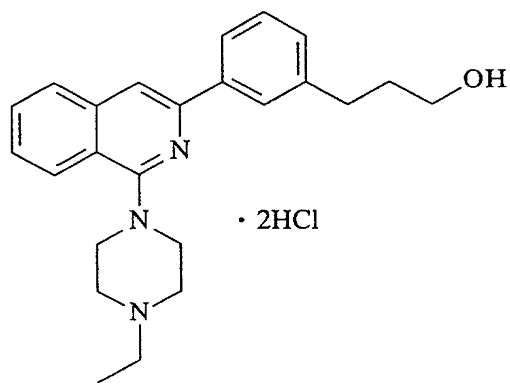
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 3.20-3.29(m,2H), 3.36(br-q,2H), 3.51(br-t,2H), 3.64(br-d,2H),

3.78-3.83(m,12H), 4.02(br-d,2H), 7.43(br-d,1H), 7.62(br-t,1H), 7.76(br-t,1H), 7.96(d,J=8.4Hz,1H), 8.13(d,J=8.4Hz,1H), 8.16(s,1H), 8.46-8.53(m,2H), 10.76(m,1H).

m.p.; 162-164°C

MS(FAB) m/z 403(M+H)$^+$.

Example 418 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[3-(3-hydroxypropyl)phenyl]isoquinoline



Ethyl 3-(3-bromophenyl)propionate (3.3 g) and hexabutylditin (7.5 g) were reacted in xylene (50 ml) in the presence of tetrakistriphenylphosphinepalladium(0) (0.50 g) at 140°C for 1.5 hr. After the reaction solution was back to room temperature, it was directly subjected to silica gel column chromatography (ethyl acetate/hexane system), to give 1-(2-ethoxycarbonylethyl)-3-tributylstannylbenzene (2.70g) as a pale yellow oil. Further, the resulting compound was reacted as it was with 1-(4-ethylpiperazin-1-yl)-3-bromoisoquinoline (1.13 g) in xylene (30 ml) in the presence of tetrakistriphenylphosphinepalladium(0) (0.3 g) at 140°C for 4 hr. The reaction solution was extracted with a 2N aqueous

solution of hydrochloric acid (20 ml) and basified again with sodium carbonate, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 1-(4-ethylpiperazin-1-yl)-3-[3-(2-ethoxycarbonylethyl)phenyl]isoquinoline (0.85 g) as a pale yellow oil.

A solution of 1-(4-ethylpiperazin-1-yl)-3-[3-(2-(2-ethoxycarbonylethyl)phenyl)isoquinoline (0.85 g) in tetrahydrofuran (10 ml) was added dropwise into a suspension of lithium aluminum hydride (0.1 g) in tetrahydrofuran (30 ml) at room temperature, and the mixture was stirred for 30 min. The reaction mixture was cooled, water (1 ml), a 5N aqueous solution of sodium hydroxide (1 ml) and water (3 ml) were sequentially added thereto, and then the mixture was stirred at room temperature for 1 hr. After the resulting precipitates were filtered off and washed with ethyl acetate, the resulting filtrate was concentrated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the title compound (0.51 g) as a pale yellow oil.

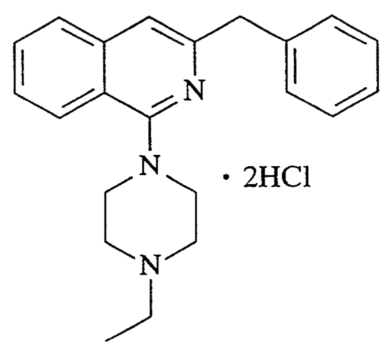
The resulting compound was converted into a hydrochloride in a conventional manner, to give a yellow powder (0.50 g). Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 1.76-1.85(m,2H), 2.75(br-t,2H), 3.19-3.28(m,2H), 3.30-3.41(m,2H), 3.47(t,J=7.2Hz,3H), 3.52(br-t,2H), 3.64(br-d,2H), 4.00(br-d,2H), 7.26(d,J=8.0Hz,1H), 7.42(t,J=8.0Hz,1H), 7.61(br-t,1H), 7.75(br-t,1H), 7.98-8.04(m,3H), 8.10(s,1H), 7.99(d,J=8.0Hz,1H), 8.12(br-d,1H).

m.p.; 101-103°C

MS(FAB) m/z 376(M+H)$^+$.

Example 419 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-benzylisoquinoline



To a mixture solution of 1-(4-ethylpiperazin-1-yl)-3-bromoisoquinoline (0.71 g) cooled to 0°C and [1,3-bis(diphenylphosphino)propane]dichloronickel(II) (0.05 g) in diethyl ether (20 ml) was dropwise added 1M benzylmagnesium chloride/ether solution (4.5 ml) in nitrogen atmosphere. The reaction mixture was stirred at room temperature overnight. The reaction solution was diluted with ether (30 ml), washed with water and brine, and then dried over magnesium sulfate. The solvent was removed, and the resulting residue was purified by silica gel column chromatography (ethyl acetate/acetone

system), to give the title compound (0.44 g; 59.5%) as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 2.54(q,J=7.2Hz,2H), 2.73(m,4H), 3.49(m,4H), 4.12(s,2H), 6.98(s,1H), 7.19(t,J=8.0Hz,1H), 7.24-7.30(m,2H), 7.36(d,J=8.0Hz,2H), 7.40(d,J=8.0Hz,1H), 7.51(t,J=8.0Hz,1H), 7.61(d,J=8.0Hz,1H), 8.00(d,J=8.0Hz,1H).

The resulting compound was converted into a hydrochloride in a conventional manner, to give a yellow powder (0.49 g).

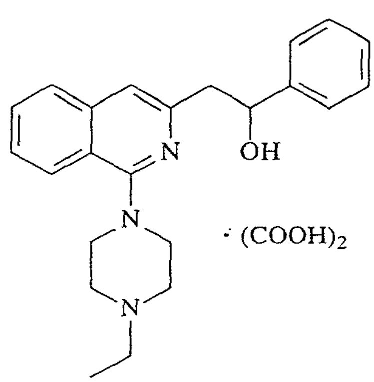
Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.36(t,J=7.2Hz,3H), 3.35(q,J=7.2Hz,2H), 3.50(br-t,2H), 3.77-3.88(m,6H), 4.26-4.34(m,4H), 4.31(s,2H), 7.26-7.40(m,6H), 7.74(dt,J=8.4,1.2Hz,1H), 7.61(d,J=8.0Hz,1H), 7.74(dt,J=8.0,0.8Hz,1H), 8.15(d,J=8.0Hz,1H).

m.p.; 118-119°C

MS(FAB) m/z 332$(M+H)^+$.

Example 420 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(2-hydroxy-2-phenylethyl)isoquinoline



A mixed solution of 1-(4-ethylpiperazin-1-yl)-3-bromoisoquinoline (1.00 g), acetophenone (1.50 g) and tert-butoxypotassium (1.40 g) in dimethyl sulfoxide (50 ml) was irradiated with light (450 W; mercury-vapor lamp) at room temperature for 5 hr. Water (200 ml) was added to the reaction solution, and the mixture was extracted with ethyl acetate. The resulting organic layer was washed with water and brine, and then extracted with a 2N aqueous solution of hydrochloric acid (100 ml). The resulting aqueous layer was basified with sodium carbonate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine, and dried over magnesium sulfate. The solvent was removed, to give 1-(4-ethylpiperazin-1-yl)-3-phenacylisoquinoline (1.0 g) as a pale yellow oil.

To a solution of the resulting 1-(4-ethylpiperazin-1-yl)-3-phenacylisoquinoline (0.92 g) in methanol (30 ml) was added sodium borohydride (0.12 g) at room temperature. One hr later, the reaction mixture was concentrated. The resulting residue was partitioned between ethyl acetate and water, and extracted with ethyl acetate. The resulting organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was removed, to give the title compound (0.81 g) as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.77(m,4H), 3.14(d,J=6.8Hz,2H),

3.55(m,4H), 5.15(br-t,1H), 6.75(br-s,1H), 7.02(s,1H), 7.22-7.28(m,1H), 7.35(t,J=8.0Hz,2H), 7.42-7.49(m,3H), 7.58(t,J=8.0Hz,1H), 7.65(d,J=8.0Hz,1H), 8.05(d,J=8.0Hz,1H).

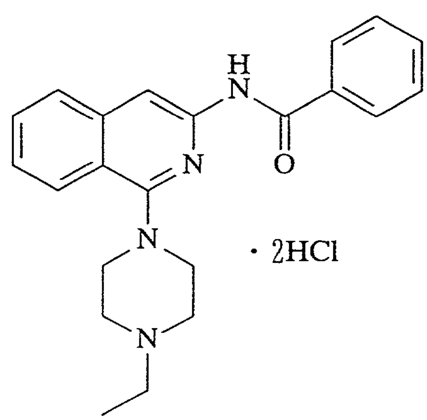
The resulting compound was converted into an oxalate in a conventional manner, to give a pale yellow powder (0.88 g).

Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.26(t,J=7.2Hz,3H), 3.00-3.64(m,12H), 5.08(t,J=6.8Hz,1H), 7.19-7.37(m,6H), 7.56(t,J=8.0Hz,1H), 7.68(t,J=8.0Hz,1H), 7.80(d,J=8.0Hz,1H), 8.07(d,J=8.0Hz,1H).

Melting point; 148-149 °C

Example 421 Synthesis of 3-benzamide-1-(4-ethylpiperazin-1-yl)isoquinoline



To a suspension of α-cyanotolunitrile (20.0 g) in acetic acid (50 ml) was added 25% hydrogen bromide/acetate solution (150 ml), and the mixture was reacted at room temperature overnight. The resulting precipitates were collected by filtration and then added to a 10% aqueous solution of potassium carbonate. The yellow powder was changed to a pale yellow

powder. The resulting powder was collected by filtration, washed with water and hexane, and dried at 50°C under reduced pressure, to give 3-amino-1-bromoisoquinoline (28.5 g; 90.8%).

3-Amino-1-bromoisoquinoline (10.3 g) and 1-ethylpiperazine (10.5 g) were reacted in the presence of potassium carbonate (13.8 g) in N,N-dimethylformamide (80 ml) at room temperature for 3 days. The reaction solution was concentrated, followed by the addition of purified water (500 ml), and the resulting mixture was stirred under ice-cooling for 1 hr. The resulting ocherous precipitates were collected by filtration, washed with a small amount of ice-water and hexane, and then dried at 50°C under reduced pressure, to give 3-amino-1-(4-ethylpiperazin-1-yl)isoquinoline (4.5 g).

To a solution of 3-amino-1-(4-ethylpiperazin-1-yl)isoquinoline (0.5 g) in pyridine (10 ml) was added benzoyl chloride (0.28 g), and the mixture was reacted at room temperature for 5 hr. The reaction solution was concentrated, and then extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine, and dried over magnesium sulfate. The solvent was removed, and the resulting residue was purified by NH-silica gel column chromatography (ethyl acetate/hexane system), to give the title compound (0.57 g, %) as a pale yellow solid.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.73(m,4H), 3.45(m,4H),

7.36(t,J=8.0Hz,1H), 7.48-7.60(m,4H), 7.78(d,J=8.0Hz,1H), 7.93-8.02(m,3H), 8.27(s,1H), 8.38(s,1H).

The resulting title compound was converted into a hydrochloride in a conventional manner, to give a yellow powder (0.58 g).

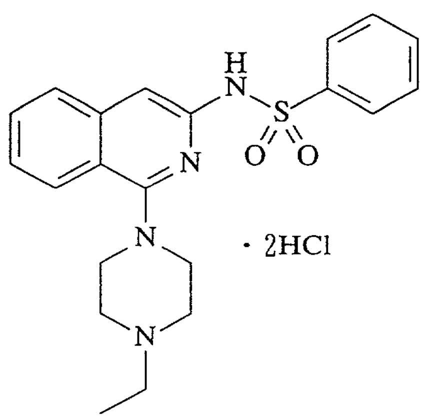
Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.32(t,J=7.2Hz,3H), 3.14-3.38(m,4H), 3.48-3.60(m,4H), 3.92(br-d,2H), 7.45-7.68(m,5H), 7.89(d,J=8.4Hz,1H), 7.98-8.08(m,3H), 8.21(s,1H), 10.45(s,1H), 11.15(m,1H).

m.p.; 160-162°C

MS(FAB) m/z 362(M+H)$^+$.

<u>Example 422 Synthesis of 3-benzenesulfoneamide-1-(4-ethylpiperazin-1-yl)isoquinoline</u>



To a solution of 3-amino-1-(4-ethylpiperazin-1-yl)isoquinoline (0.4 g) in pyridine (10 ml) was added benzoylsulfonyl chloride (0.29 g), and the mixture was stirred at room temperature for 5 hr. The reaction solution was concentrated, and then extracted with ethyl acetate. The ethyl

acetate layer was washed with water and brine, and then dried over magnesium sulfate. The solvent was removed, and the resulting residue was purified by NH-silica gel column chromatography (ethyl acetate/hexane system), to give the title compound (0.48 g) as a pale yellow solid.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.14(t,J=7.2Hz,3H), 2.48(q,J=7.2Hz,2H), 2.62(m,4H), 3.35(m,4H), 7.16(s,1H), 7.33(br-t,1H), 7.42(br-t,2H), 7.48-7.53(m,2H), 7.64(d,J=8.0Hz,1H), 7.88-7.94(m,2H).

The resulting title compound was converted into a hydrochloride in a conventional manner, to give a yellow amorphous (0.54 g).

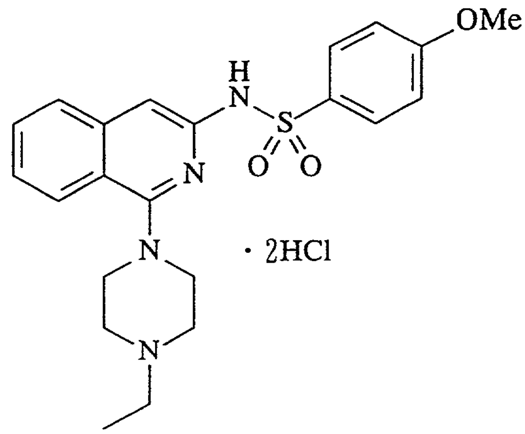
Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.32(t,J=7.2Hz,3H), 3.15-3.26(m,2H), 3.27-3.39(m,2H), 3.48-3.60(m,4H), 3.94(br-d,2H), 7.48-7.71(m,5H), 7.90(d,J=8.0Hz,1H), 8.00-8.08(m,3H), 8.23(s,1H), 10.45(s,1H), 10.98(m,1H).

m.p.; amorphous

MS(ESI) m/z 397$(M+H)^+$.

<u>Example 423</u> <u>Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(4-methoxybenzenesulfonamide)isoquinoline</u>



To a solution of 3-amino-1-(4-ethylpiperazin-1-yl)isoquinoline (0.4 g) in pyridine (10 ml) was added 4-methoxybenzenesulfonyl chloride (0.33 g), and the mixture was reacted at room temperature for 5 hr. The reaction solution was concentrated, and then extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine, and then dried over magnesium sulfate. The solvent was removed, and the resulting residue was purified by NH-silica gel column chromatography (ethyl acetate/hexane system), to give the title compound (0.52 g, %) as a pale yellow solid.

Free compound:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.05(t,J=7.2Hz,3H), 2.38(q,J=7.2Hz,2H), 2.50(m,4H), 3.20(m,4H), 3.79(s,3H), 6.87(s,1H), 7.05(d,J=8.0Hz,2H), 7.36(br-t,1H), 7.55(br-t,2H), 7.68(d,J=8.0Hz,1H), 7.84(d,J=8.0Hz,2H), 7.80-7.88(m,1H), 10.54(m,1H).

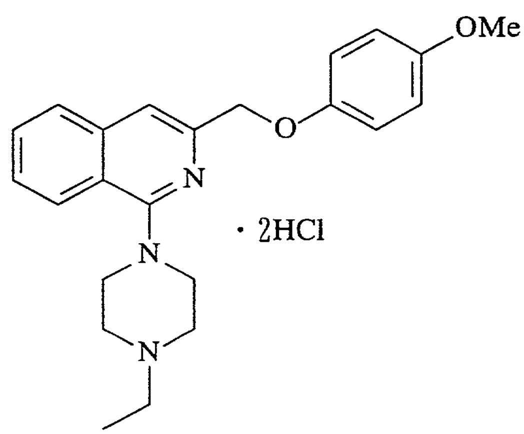
The resulting title compound was converted into a hydrochloride in a conventional manner, to give a pale yellow amorphous (0.59 g).

Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.30(t,J=7.2Hz,3H), 3.10-3.25(m,2H), 3.40(br-t,2H), 3.51(br-d,2H), 3.71(br-d,2H), 3.79(s,3H), 6.98(s,1H), 7.11(d,J=9.2Hz,2H), 7.40(br-t,1H), 7.60(br-t,1H), 7.76(d,J=8.0Hz,1H), 7.87(d,J=9.2Hz,2H), 7.93(br-d,1H), 10.80(s,1H), 11.09(m,1H).

MS(ESI) m/z 427$(M+H)^+$.

Example 424 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(4-methoxyphenoxymethyl)isoquinoline hydrochloride



A solution of 4-(4-ethylpiperidin-1-yl)-3-bromoisoquinoline (1.03 g) in tetrahydrofuran (20 ml) was cooled to -78 °C, followed by the dropwise addition of 1.7M tert-butyllithium (3 ml). Fifteen minutes later, N,N-dimethylformamide (0.5 ml) was added thereto and the temperature of the reaction solution was raised to room temperature. To the reaction solution was added an aqueous solution of ammonium chloride, and the mixture was extracted with ethyl acetate, followed by washing with water and brine, drying and evaporating. The resulting residue was dissolved

in methanol (15 ml), and reacted with sodium borohydride (0.4 g). The solvent was removed, the resulting residue was extracted with ethyl acetate extraction, followed by washing with water and brine, drying and evaporating. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 4-(4-ethylpiperidin-1-yl)-3-hydroxymethylisoquinoline (0.46 g, 52.7%) as a pale yellow oil.

A solution of 4-(4-ethylpiperazin-1-yl)-3-hydroxymethylisoquinoline (0.25 g), 4-methoxyphenol (0.12 g) and triphenylphosphine (0.29 g) in tetrahydrofuran (20 ml) was cooled to -30°C, followed by the dropwise addition of diethyl azodicarboxylate (0.19 g). The temperature of the reaction was raised gradually to room temperature, and the reaction was conducted for further 12 hr. The reaction solution was diluted with ethyl acetate (50 ml) and extracted with a 2N aqueous solution of hydrochloric acid. Then the mixture was basified with a 5N aqueous solution of sodium hydroxide and extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine, dried and evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the title compound (0.21 g) as a pale yellow oil.

The resulting title compound was converted into a hydrochloride in a conventional manner, to give a yellow powder (0.18 g).

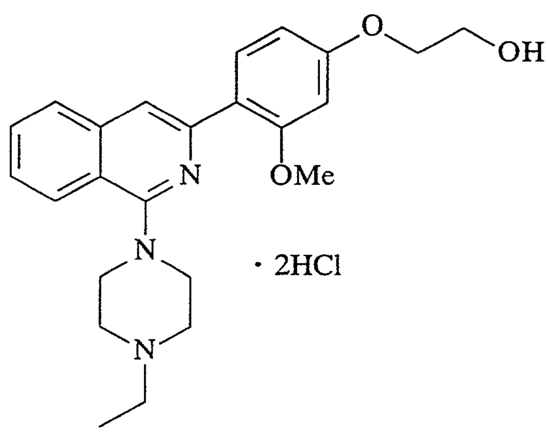
Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.32(t,J=7.2Hz,3H), 3.16-3.38(m,4H), 3.45(br-t,2H), 3.59(br-d,2H), 3.69(s,3H), 3.89(br-d,2H), 5.15(s,2H), 6.88(dd,J=8.8,1.6Hz,2H), 7.02(dd,J=8.8,1.6Hz,2H), 7.57(s,1H), 7.62(br-t,1H), 7.74(br-t,1H), 7.94(d,J=8.0Hz,1H), 8.12(d,J=8.4Hz,1H).

m.p.; 101-102°C

MS(ESI) m/z 378(M+H)$^+$.

Example 425 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxyethoxy)-2-methoxyphenyl]isoquinoline



According to Example 36-1, N-methyl-o-toluamide (1.70 g) and 4-(2-benzyloxyethoxy)-2-methoxybenzonitrile (3.30 g) were reacted, to give 3-[4-(2-benzyloxyethoxy)-2-methoxyphenyl]isoquinolin-1-one (0.47 g).

The resulting 3-[4-(2-benzyloxyethoxy)-2-methoxyphenyl]isoquinolin-1-one (0.47 g) was added to phosphorus oxychloride (10 ml), and the mixture was reacted at room temperature overnight. The reaction solution was evaporated, and to the resulting residue were added ethyl

acetate and purified water. The ethyl acetate layer was washed with water, an aqueous solution of sodium bicarbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting 1-chloro-3-[4-(2-benzyloxyethoxy)-2-methoxyphenyl]isoquinoline was reacted as it was with N-ethylpiperazine (5 ml) in the presence of potassium carbonate (1.2 g) at 120°C for 24 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and purified water. The ethyl acetate layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by NH-silica gel column chromatography (ethyl acetate/hexane system), to give 1-(4-ethylpiperazin-1-yl)-3-[4-(2-benzyloxyethoxy)-2-methoxyphenyl]isoquinoline hydrochloride (0.11 g) as a yellow powder.

1-(4-Ethylpiperazin-1-yl)-3-[4-(2-benzyloxyethoxy)-2-methoxyphenyl]isoquinoline hydrochloride (0.10 g) was dissolved in methanol (20 ml), followed by the hydrogenation in the presence of 10% palladium/carbon catalyst (0.03 g) at room temperature for 6 hr. The catalyst was filtered off. The resulting solution was washed with methanol, and then the filtrate was evaporated. The resulting residue was crystallized from ethanol/ether, to give the title compound (0.04 g) as a yellow powder.

Hydrochloride:

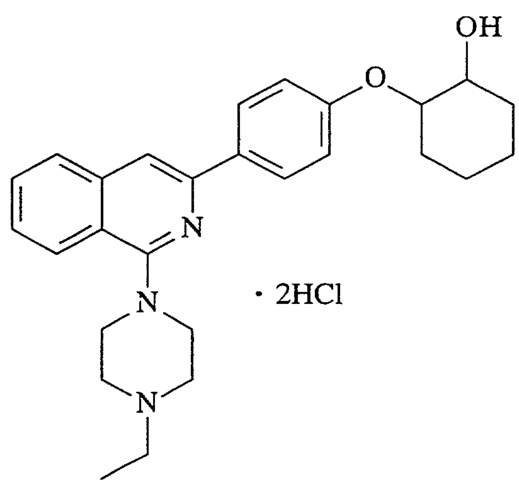
^{1}H-NMR(400MHz,D_2O) ; δ (ppm) 1.37(t,J=7.2Hz,3H),

3.35(q,J=7.2Hz,2H), 3.42-3.60(m,2H), 3.70-3.95(m,6H), 3.92(s,3H), 4.16(m,2H), 4.25(br-d,2H), 6.70(s+d,2H), 7.57(d,J=8.0Hz,1H), 7.66(s,1H), 7.72-7.77(m,1H), 7.94(m,2H), 8.10(d,J=8.4Hz,1H).

m.p.; 140-142°C

MS(FAB) m/z 408(M+H)$^+$.

Example 426 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxycyclohexyloxy)phenyl]isoquinoline hydrochloride



1-(4-Ethylpiperazin-1-yl)-3-(4-hydroxyphenyl)isoquinoline (380 mg) obtained in Example 7 was dissolved in tetrahydrofuran (20 ml), followed by the addition of 60% oily sodium hydride (48 mg) at room temperature. Thirty minutes later, the solvent was removed. To the resulting residue was added cyclohexene oxide (15 ml), and the mixture was reacted at 150°C for 3 hr. After cooling, the reaction solution was diluted with ethyl acetate and extracted with a 5N aqueous solution of hydrochloric acid. The aqueous layer was basified with a 8N aqueous solution of sodium hydroxide and

extracted with ethyl acetate. The organic phase was washed with water and brine, and dried over magnesium sulfate. The solvent was removed, and the resulting residue was purified by NH-silica gel column chromatography (ethyl acetate/hexane system), to give the free compound of the title compound as a pale yellow oil.

The resulting free compound was converted into a hydrochloride in a conventional manner, to give the title compound (240 mg) as a yellow powder.

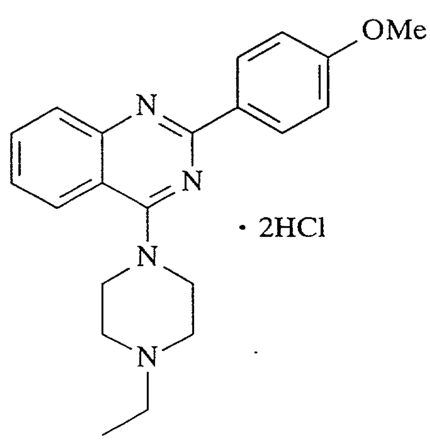
Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.23-1.42(m,7H), 1.59-1.68(m,2H), 1.85-1.94(m,1H), 2.00-2.08(m,1H), 3.20-3.66(m,9H), 3.97(br-d,2H), 4.10-4.20(m,1H), 7.07(d,J=8.0Hz,2H), 7.52-7.61(m,1H), 7.66-7.75(m,1H), 7.90-8.14(m,5H), 10.82(m,1H).

m.p.; 143-144°C

MS(ESI) m/z 432(M+H)$^+$.

Example 427 Synthesis of 4-(4-ethylpiperazin-1-yl)-2-(4-methoxyphenyl)quinazoline dihydrochloride



A mixture of 4-(1-ethylpiperazin-4-yl)-2-

chloroquinazoline (0.56 g), 4-methoxyphenylboric acid (0.46 g), tetrakistriphenylphosphinepalladium(0) (0.12 g), toluene (50 ml) and a 10% aqueous solution of sodium carbonate (30 ml) was vigorously stirred in nitrogen atmosphere at 100°C for 1 hr. To the resulting mixture was additionally added 4-methoxyphenylboric acid (0.31 g), and the mixture was further stirred for 2 hr. To the resulting mixture was again added 4-methoxyphenylboric acid (0.31 g), and the mixture was further stirred for 1 hr. To the resulting mixture was further added 4-methoxyphenylboric acid (0.31 g), and the mixture was further stirred overnight. The resulting insoluble matters were filtered off, and then the organic layer was separated and extracted with 2N hydrochloric acid twice, followed by the addition of a 8N aqueous solution of sodium hydroxide to adjust the resulting mixture to pH 10. The resulting mixture was extracted with ethyl acetate twice. The extract was washed with brine and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by NH silica gel column chromatography (ethyl acetate/n-hexane system), to give 0.58 g of the free compound of the title compound as a pale yellow viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 2.53(q,J=7.2Hz,2H), 2.70(t,J=5.0Hz,4H), 3.89(s,3H), 3.90(t,J=5.0Hz,4H), 7.00(d,J=8.8Hz,2H), 7.37(ddd,J=1.2,8.4,8.4Hz,1H), 7.70(ddd,J=1.2,8.4,8.4Hz,1H),

7.88(dd,J=1.2,8.4Hz,1H), 7.93(dd,J=1.2,8.4Hz,1H), 8.51(d,J=8.8Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/IPE, to give the title compound as a yellow powder.

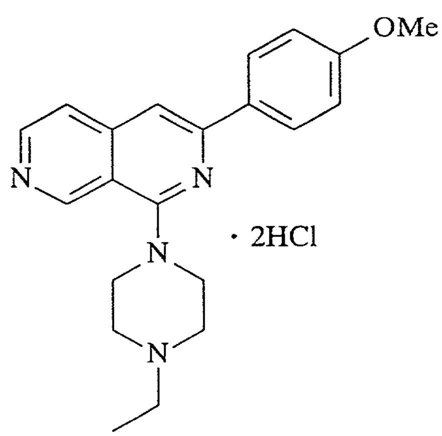
Hydrochloride:

m.p.; 224.5-226°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.31(t,J=7.2Hz,3H), 3.15-3.21(m,2H), 3.24-3.32(m,2H), 3.65(br-d,2H), 4.03(br-s,2H), 4.84(br-s,2H), 7.19(d,J=8.8Hz,2H), 7.67(br-t,1H), 8.02(br-t,1H), 8.20(br-d,1H), 8.28(br-s,1H), 8.54(d,J=8.8Hz,2H), 11.64(br-s,1H).

MS(ESI) m/z 349(M+H)$^+$.

Example 428 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(4-methoxyphenyl)-7-azaisoquinoline



4-Chloro-3-cyanopyridine (1.50 g) and 4-methoxyphenylacetylene (1.60 g) were reacted in the presence of dichlorobistriphenylphosphinepalladium (0.14 g), cuprous iodide (75 mg) and triethylamine (10 ml) in N,N-

dimethylformamide (25 ml) in nitrogen atmosphere at 100°C overnight. The reaction mixture was poured into water (100 ml), and the mixture was extracted with ethyl acetate. The resulting organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give 4-(4-methoxyphenylethynyl)-3-cyanopyridine (2.13 g, 95 %) as a pale yellow oil.

4-(4-Methoxyphenylethynyl)-3-cyanopyridine (2.10 g) was reacted in polyphosphoric acid (10 ml) at 120°C for 15 min. Water (40 ml) was added to the reaction mixture, and then the mixture was adjusted to pH 6.5 by potassium carbonate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine, and dried over magnesium sulfate. The solvent was removed, ammonium acetate (10 g) was added to the resulting residue, and the mixture was reacted at 140°C overnight. After cooling, the reaction solution was diluted with water (100 ml) and extracted with dichloroethane. The resulting organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was removed, to give 3-(4-methoxyphenyl)-7-aza-2H-dihydroisoquinolin-1-one acetate (1.70 g, 58%).

3-(4-Methoxyphenyl)-7-aza-2H-dihydroisoquinolin-1-one acetate (0.25 g) was reacted with phosphorus oxychloride (10 g) at 100°C for 4 hr. The mixture was concentrated, followed

by the addition of water, neutralization with potassium carbonate and extraction with ethyl acetate. The organic layer was washed with water and brine, and dried over magnesium sulfate. The organic layer was filtered through silica gel and washed with ethyl acetate. The resulting filtrate was concentrated, to give 1-chloro-3-(4-methoxyphenyl)-7-azaisoquinoline (0.12 g). 1-Ethylpiperidine (10 ml) and potassium carbonate (0.5 g) were added thereto, and the mixture was reacted at 80°C for 6 hr. The reaction mixture was evaporated, and the resulting residue was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with water and brine, and dried over magnesium sulfate. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound (0.10 g, 65%) as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.75(m,4H), 3.70(m,4H), 3.88(s,3H), 7.01(d,J=8.0Hz,2H), 7.48(s,1H), 7.52(d,J=8.0Hz,1H), 8.12(d,J=8.0Hz,2H), 8.54(d,J=8.0Hz,1H), 9.40(br-d,1H).

The resulting title compound was converted into a hydrochloride in a conventional manner, to give a yellow powder (0.11 g).

Hydrochloride:

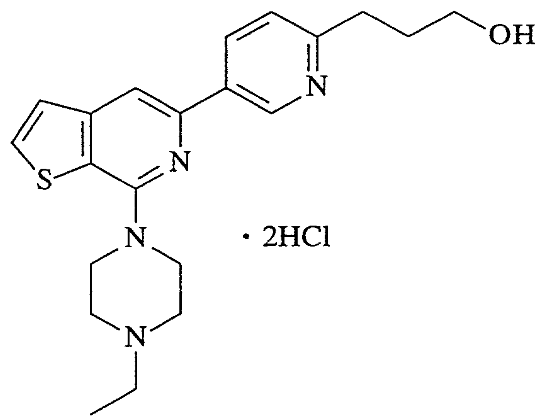
^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.33(t,J=7.2Hz,3H), 3.15-4.00(m,8H), 3.85(s,1H), 4.34(br-d,2H), 7.13(d,J=8.4Hz,2H),

8.12(s,1H), 8.16(br-d,1H), 8.24(d,J=8.4Hz,2H), 8.63(m,1H), 9.63(br-s,1H), 11.52(m,1H).

m.p.; 222°C (decomp.)

MS(ESI) m/z 349(M+H)$^+$.

Example 429 Synthesis of 7-(4-ethylpiperazin-1-yl)-5-[2-(3-hydroxypropyl)pyridin-5-yl]thieno[2,3-c]pyridine hydrochloride



3-Cyanomethyl-2-thiophenecarboxylic acid (7.50 g) was reacted in phosphorus tribromide (40 ml) at 170°C for 5 hr. The reaction was back to room temperature. Under cooling, water was added to the reaction mixture, followed by the neutralization with potassium carbonate and extraction with ethyl acetate. The organic layer was washed with water and brine, and dried over magnesium sulfate. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give 5,7-dibromothieno[2,3-c]pyridine (2.04 g, 15.5%) as a pale brown solid.

5,7-Dibromothieno[2,3-c]pyridine (2.04 g), 1-ethylpiperidine (0.95 g) and potassium carbonate (2.0 g) were

reacted in N,N-dimethylformamide (15 ml) at 70°C for 2 hr. The reaction mixture was evaporated, and the resulting residue was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with water and brine, and dried over magnesium sulfate. The resulting residue was purified by silica gel column chromatography (ethyl acetate/methanol system), to give 7-(4-ethylpiperidin-1-yl)-5-bromothieno[2,3-c]pyridine (1.95 g) as a brown oil.

5-Bromo-2-[3-(tert-butyldimethylsilyloxy)propyl]pyridine (3.26 g) and hexabutylditin (5.80 g) were heated in the presence of tetrakistriphenylphosphinepalladium(0) in xylene, to give 2-[3-(tert-butyldimethylsilyloxy)propyl]-5-tributylstannylpyridine (1.80 g).

The resulting compound and 7-(4-ethylpiperidin-1-yl)-5-bromothieno[2,3-c]pyridine (0.54 g) previously were reacted in the presence of tetrakistriphenylphosphinepalladium(0) (0.20 g) in xylene in nitrogen atmosphere for 1 hr. A 2N aqueous solution of hydrochloric acid (30 ml) was added to the reaction solution, and the mixture was stirred for 30 min. Then, the aqueous layer was separated, basified with a 5N aqueous solution of sodium hydroxide, and then back-extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine, dried and evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the title compound (0.31 g) as a pale yellow

oil.

The resulting title compound was converted into a hydrochloride in a conventional manner, to give a yellow powder (0.38 g).

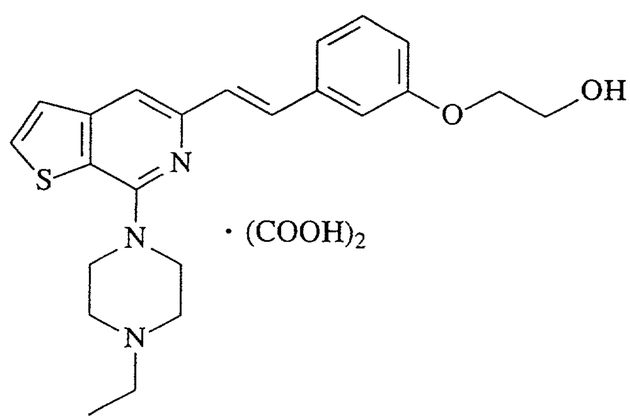
Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.32(t,J=7.2Hz,3H), 1.89-1.98(m,2H), 3.08-3.27(m,5H), 3.49(t,J=6.4Hz,2H), 3.58-3.70(m,4H), 4.48(br-d,2H), 7.62(d,J=5.2Hz,1H), 7.99(d,J=8.0Hz,1H), 8.19(d,J=5.2Hz,1H), 8.32(s,1H), 8.07(d,J=8.0Hz,1H), 9.34(br-s,1H), 11.34(m,1H).

m.p.; 204-205°C

MS(ESI) m/z 383(M+H)$^+$.

<u>Example 430 Synthesis of 7-(4-ethylpiperazin-1-yl)-5-[3-(2-hydroxyethoxy)styryl]thieno[2,3-c]pyridine hydrochloride</u>



7-(4-Ethylpiperidin-1-yl)-5-bromothieno[2,3-c]pyridine (300 mg) and 3-(2-hydroxyethoxy)styrene (300 mg) were reacted in the presence of palladium acetate (30 mg), tri-o-toluylphosphine (81 mg) and triethylamine (2 ml) in N,N-dimethylformamide (15 ml) in nitrogen atmosphere for 6 hr.

After cooling, the reaction solution was diluted with ethyl acetate (200 ml), washed with water and brine, dried and evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the title compound (100 mg) as a pale yellow oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 2.53(q,J=7.2Hz,2H), 2.69(m,4H), 3.82(m,4H), 3.98(m,2H), 4.15(m,2H), 7.01(t,J=8.0Hz,2H), 7.13(d,J=18.0Hz,1H), 7.22(s,1H), 7.21-7.25(d,1H), 7.29(d,J=5.2Hz,1H), 7.55(d,J=5.2Hz,2H), 7.65(br-d,1H), 8.07(d,J=18.0Hz,1H).

The resulting title compound was converted into an oxalate in a conventional manner, to give a white powder (57 mg).

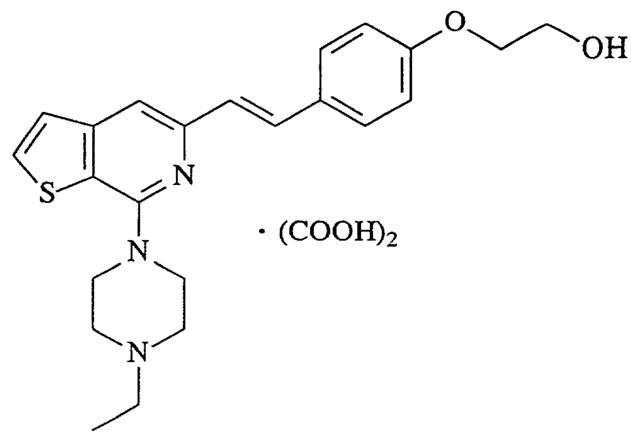
Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.25(br-t,3H), 3.04-3.80(m,10H), 3.76(br-t,2H), 4.06(br-t,2H), 6.86-6.91(m,1H), 7.19-7.36(m,3H), 7.51(s,1H), 7.54(d,J=5.2Hz,1H), 7.62(d,J=8.0Hz,1H), 8.05(d,J=5.2Hz,1H).

m.p.; 98-99°C

MS(FAB) m/z 410$(M+H)^+$.

Example 431 Synthesis of 7-(4-ethylpiperazin-1-yl)-5-[4-(2-hydroxyethoxy)styryl]thieno[2,3-c]pyridine hydrochloride



7-(4-Ethylpiperidin-1-yl)-5-bromothieno[2,3-c]pyridine (300 mg) and 4-(2-hydroxyethoxy)styrene (300 mg) were reacted in the presence of palladium acetate (30 mg), tri-o-toluylphosphine (81 mg) and triethylamine (2 ml) in N,N-dimethylformamide (15 ml) in nitrogen atmosphere for 6 hr. After cooling, the reaction solution was diluted with ethyl acetate (200 ml), washed with water and brine, dried and evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the title compound (120 mg) as a pale yellow oil.

The resulting title compound was converted into an oxalate in a conventional manner, to give a white powder (68 mg).

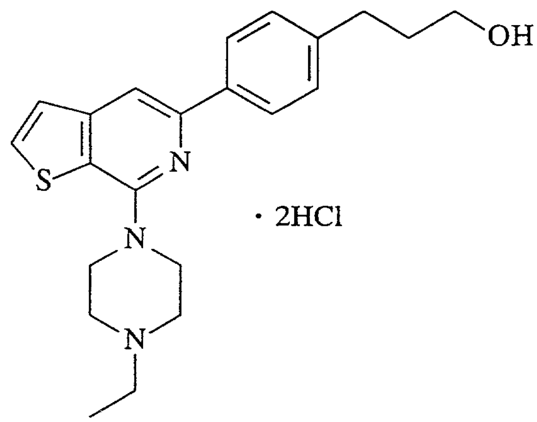
Oxalate:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.25(br-t,3H), 3.09(br-q,2H), 3.29(m,4H), 3.73(t,J=5.2Hz,1H), 3.80-3.99(m,4H), 4.02(t,J=5.2Hz,1H), 6.97(d,J=8.4Hz,2H), 7.16(d,J=12.0Hz,1H), 7.46(s,1H), 7.51(d,J=5.2Hz,1H), 7.58(d,J=8.4Hz,1H), 7.60(d,J=12.0Hz,1H), 8.03(d,J=5.2Hz,1H).

m.p.; 143-145°C

MS(ESI) m/z 410$(M+H)^+$.

Example 432 Synthesis of 7-(4-ethylpiperazin-1-yl)-5-[4-(3-hydroxypropyl)phenyl]thieno[2,3-c]pyridine hydrochloride



7-(4-Ethylpiperidin-1-yl)-5-bromothieno[2,3-c]pyridine (200 mg) and ethyl 3-(4-tributylstannylphenyl)propionate (400 mg) were reacted in the presence of tetrakistriphenylphosphinepalladium(0) (50 mg) in xylene (10 ml) in nitrogen atmosphere for 5 hr. After cooling, the reaction solution was diluted with ethyl acetate (200 ml) and extracted with a 2N aqueous solution of hydrochloric acid. The resulting solution was basified with a 5N aqueous solution of sodium hydroxide and extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine, dried and evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 7-(4-ethylpiperazin-1-yl)-5-[4-(ethoxycarbonylethyl)phenyl]thieno[2,3-c]pyridine (0.20 g) as a pale yellow oil.

The resulting compound (0.20 g) was dissolved in

tetrahydrofuran (5 ml), and added dropwise into a suspension of lithium aluminum hydride (0.07 g) in tetrahydrofuran (20 ml) at room temperature. The reaction mixture was stirred for 1 hr, followed by the sequential addition of water (0.07 ml), a 5N aqueous solution of sodium hydroxide (0.07 ml) and water (0.21 ml), and the mixture was stirred at room temperature for 1 hr. The resulting precipitates were filtered off, while the resulting filtrate was washed with ethyl acetate. The filtrate was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the title compound as a pale yellow oil (0.12 g).

The resulting title compound was converted into a hydrochloride in a conventional manner, to give a yellow powder (0.10 g).

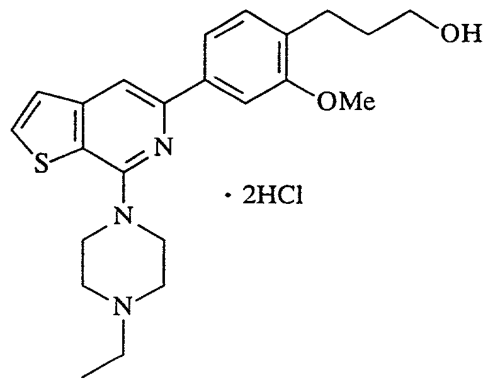
Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.31(t,J=7.2Hz,3H), 1.71-1.80(m,2H), 2.67(t,J=7.2Hz,2H), 3.14-3.26(m,4H), 3.44(t,J=7.2Hz,2H), 3.55(br-t,2H), 3.64(br-d,2H), 4.43(br-d,2H), 7.32(d,J=8.0Hz,2H), 7.56(d,J=5.6Hz,1H), 8.01(s,1H), 8.05(d,J=8.0Hz,2H), 8.07(d,J=5.6Hz,1H), 10.82(m,1H).

m.p.; 112-113°C

MS(FAB) m/z 382(M+H)$^+$.

Example 433 Synthesis of 7-(4-ethylpiperazin-1-yl)-5-[4-(3-hydroxypropyl)-3-methoxyphenyl]thieno[2,3-c]pyridine hydrochloride



5-Bromo-2-(3-acetoxypropyl)anisole (2.27 g) and hexabutylditin (5.28 g) were heated in the presence of tetrakistriphenylphosphinepalladium(0) in xylene, to give 2-(3-acetoxypropyl)-5-tributylstannylanisole (0.92 g).

The resulting compound and 7-(4-ethylpiperidin-1-yl)-5-bromothieno[2,3-c]pyridine (0.21 g) were reacted in the presence of tetrakistriphenylphosphinepalladium(0) (0.12 g) in xylene in nitrogen atmosphere for 1 hr. The reaction solution was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 7-(4-ethylpiperazin-1-yl)-5-[4-(3-acetoxypropyl)-3-methoxyphenyl]thieno[2,3-c]pyridine (42 mg) as a pale yellow oil.

The resulting compound was dissolved in methanol (15 ml), and reacted with a 2N aqueous solution of sodium hydroxide (5 ml) at room temperature overnight. The reaction solution was concentrated, and the resulting residue was extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, to give the free compound of the title compound.

The resulting free compound was converted into a hydrochloride in a conventional manner, to give 31 mg of the title compound as a yellow powder.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17-1.25(m,3H), 1.80-1.92(m,2H), 2.62(m,2H), 2.68-2.84(m,6H), 3.63(m,2H), 3.83-3.98(m,4H), 3.95(s,3H), 7.22(d,J=8.0Hz,1H), 7.36(d,J=5.2Hz,1H), 7.58(m,2H), 7.67(s,2H).

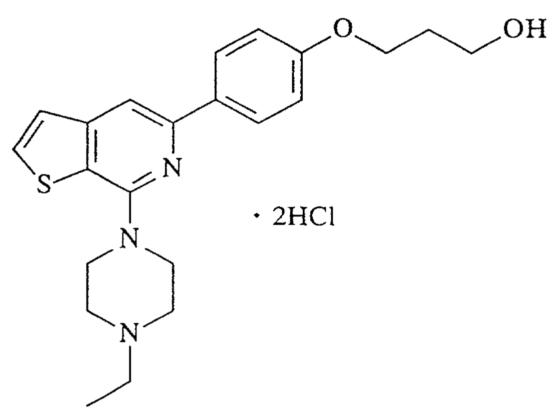
Hydrochloride:

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.31(t,J=7.2Hz,3H), 1.66-1.75(m,2H), 2.62(t,J=7.6Hz,2H), 3.14-3.25(m,4H), 3.44(q,J=6.4Hz,2H), 3.55-3.68(m,4H), 3.91(s,3H), 4.43(br-d,2H), 7.23(d,J=8.0Hz,1H), 7.57(d,J=5.2Hz,1H), 7.65(dd,J=8.0,1.6Hz,1H), 7.69(br-s,1H), 8.06(s,1H), 8.08(d,J=5.2Hz,1H), 11.10(m,1H).

m.p.; 114-115℃

MS(FAB) m/z 412$(M+H)^+$.

Example 434 Synthesis of 7-(4-ethylpiperazin-1-yl)-5-[4-(3-hydroxypropoxy)phenyl]thieno[2,3-c]pyridine dihydrochloride



In the same manner as in Example 161-2, 1-[4-(tributylstannyl)phenoxy]-3-(tetrahydropyran-2-YL)oxypropane (1.73 g) was obtained as a colorless oil from 1-(4-bromophenoxy)-3-(tetrahydropyran-2-yloxy)propane (2.08 g) and bis(tributyltin) (3.3 ml).

The resulting compound and 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (0.29 g) were reacted in the same manner as in Example 300-4, to give a reaction solution containing 7-(4-ethylpiperazin-1-yl)-5-[4-[3-(tetrahydropyran-2-yl)oxypropoxy]phenyl]thieno[2,3-c]pyridine. Ethyl acetate and 2N hydrochloric acid were added to the reaction solution, and the resulting insoluble matters were filtered off. The aqueous layer was separated, while the organic layer was extracted with 2N hydrochloric acid. The aqueous layers were combined and washed with ethyl acetate thrice. The pH of the resulting solution was adjusted to pH 10 by adding a 8N aqueous solution of sodium hydroxide thereto, and the resulting solution was extracted with ethyl acetate thrice. The extract was washed with brine and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by NH silica gel column chromatography (ethyl acetate/n-hexane system), to give 0.26 g of the free compound of the title compound as a colorless amorphous.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H),

2.09(quintet,J=5.9Hz,2H), 2.52(q,J=7.2Hz,2H), 2.69(t,J=5.0Hz,4H), 3.85(t,J=5.0Hz,4H), 3.90(t,J=5.9Hz,2H), 4.20(t,J=5.9Hz,2H), 6.99(d,J=9.2Hz,2H), 7.33(d,J=5.6Hz,1H), 7.55(d,J=5.6Hz,1H), 7.61(s,1H), 8.04(d,J=9.2Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a pale yellow powder.

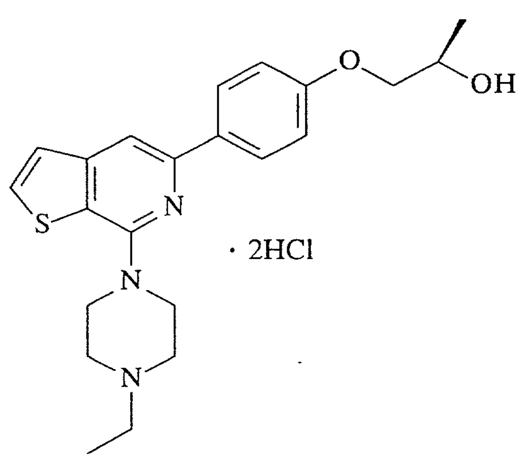
Hydrochloride:

m.p.; 126-127°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.31(t,J=7.2Hz,3H), 1.89(quintet,J=6.2Hz,2H), 3.16-3.23(m,4H), 3.53-3.66(m,4H), 3.58(t,J=6.2Hz,2H), 4.10(t,J=6.2Hz,2H), 3.42(br-d,2H), 7.04(d,J=8.8Hz,2H), 7.54(d,J=5.2Hz,1H), 7.96(s,1H), 8.05-8.09(m,3H), 10.99(br-s,1H).

MS(FAB) m/z 398(M+H)$^+$.

Example 435 Synthesis of 7-(4-ethylpiperazin-1-yl)-5-[4-(2-hydroxypropoxy)phenyl]thieno[2,3-c]pyridine dihydrochloride



In the same manner as in Example 161-2, 2-(R)-

acetoxy-1-[4-(tributylstannyl)phenoxy]propane (1.31 g) was obtained as a colorless oil from 2-(R)-acetoxy-1-(4-bromophenoxy)propane (1.94 g) and bis(tributyltin) (3.6 ml).

The resulting compound and 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (0.29 g) were reacted in the same manner as in Example 300-4, to give a reaction solution containing 7-(4-ethylpiperazin-1-yl)-5-{4-[2-(R)-acetoxypropoxy]phenyl}thieno[2,3-c]pyridine. Ethyl acetate and 2N hydrochloric acid were added to the reaction solution, and the resulting insoluble matters were filtered off. The aqueous layer was separated, while the organic layer was extracted with 2N hydrochloric acid. The aqueous layers were combined and washed with ethyl acetate twice. The pH of the resulting solution was adjusted to pH 10 by adding a 8N aqueous solution of sodium hydroxide thereto, and subsequently, methanol was added thereto until the reaction solution became homogenous. The reaction solution was left as it was at room temperature for 45 min. The solvent was evaporated, and then water was added thereto and the mixture was extracted with ethyl acetate thrice. After washing with brine and drying over magnesium sulfate, the solvent was evaporated. The resulting residue was purified by NH silica gel column chromatography (ethyl acetate/n-hexane system), to give 0.22 g of the free compound of the title compound as a colorless viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H),

1.31(d,J=6.4Hz,3H), 2.37(br-s,1H), 2.52(q,J=7.2Hz,2H), 2.69(t,J=5.0Hz,4H), 3.84-3.88(m,5H), 4.01(dd,J=3.2,9.2Hz,1H), 4.19-4.28(m,1H), 7.00(d,J=8.8Hz,2H), 7.33(d,J=5.4Hz,1H), 7.55(d,J=5.4Hz,1H), 7.62(s,1H), 8.05(d,J=8.8Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a yellow powder.

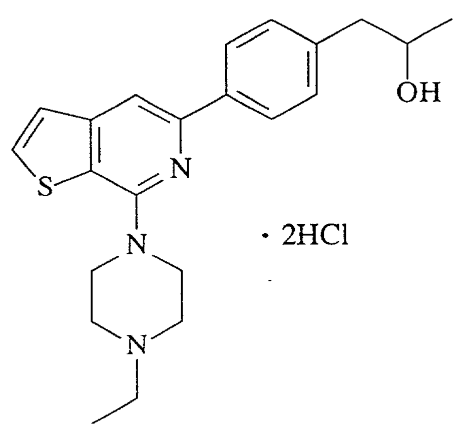
Hydrochloride:

m.p.; 126-127°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.18(d,J=6.4Hz,3H), 1.31(t,J=7.2Hz,3H), 3.16-3.24(m,2H), 3.55(br-t,2H), 3.64(br-d,2H), 3.84(dd,J=5.2,9.6Hz,1H), 3.89(dd,J=6.0,9.6Hz,1H), 3.95-4.01(m,1H), 4.42(br-d,2H), 7.05(d,J=8.8Hz,2H), 7.54(d,J=5.6Hz,1H), 7.97(s,1H), 8.05-8.09(m,3H), 10.91(br-s,1H).

MS(FAB) m/z 398(M+H)$^+$.

<u>Example 436</u> <u>Synthesis of 7-(4-ethylpiperazin-1-yl)-5-[4-(2-hydroxypropyl)phenyl]thieno[2,3-c]pyridine dihydrochloride</u>



In the same manner as in Example 161-2, 1-[4-(tributylstannyl)phenyl]propan-2-one (1.98 g) was obtained as a colorless oil from 1-(4-bromophenyl)propan-2-one (2.09 g) and bis(tributyltin) (5.0 ml).

The resulting compound and 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (0.29 g) were reacted in the same manner as in Example 300-4, to give 7-(4-ethylpiperazin-1-yl)-5-[4-(2-oxypropyl)phenyl]thieno[2,3-c]pyridine (0.20 g).

Then, the resulting 7-(4-ethylpiperazin-1-yl)-5-[4-(2-oxopropyl)phenyl]thieno[2,3-c]pyridine (0.20 g) was dissolved in tetrahydrofuran (5 ml). The resulting solution was added to a suspension of lithium aluminum hydride (0.04 g) in tetrahydrofuran (1 ml) under cooling with a cooler of sodium chloride/ice. Further, the resulting mixture was stirred for 15 min. Water (40 ml), a 5N aqueous solution of sodium hydroxide (40 ml) and water (120 ml) were sequentially added to the reaction solution, which was then diluted with ethyl acetate, and the resulting precipitates were filtered off. The solvent was evaporated, and the resulting residue was purified by NH silica gel column chromatography (ethyl acetate/n-hexane system), to give 0.15 g of the free compound of the title compound as a colorless viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 1.27(d,J=6.0Hz,3H), 2.52(q,J=7.2Hz,2H), 2.68(t,J=5.0Hz,4H), 2.75(dd,J=8.0,13.6Hz,1H), 2.84(dd,J=4.0,13.6Hz,1H),

3.85(t,J=5.0Hz,4H), 4.02-4.10(m,1H), 7.30(d,J=8.4Hz,2H), 7.33(d,J=5.6Hz,1H), 7.55(d,J=5.6Hz,1H), 7.65(s,1H), 8.04(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the titled compound as a pale yellow powder.

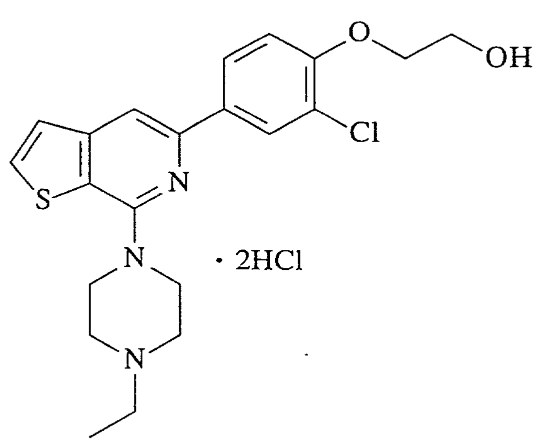
Hydrochloride:

m.p.; 66-67°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.06(d,J=6.4Hz,3H), 1.03(t,J=7.2Hz,3H), 2.62(dd,J=6.4,13.2Hz,1H), 2.75(dd,J=6.8,13.2Hz,1H), 3.17-3.23(m,2H), 3.55(br-t,2H), 3.64(br-d,2H), 3.83-3.91(m,1H), 4.43(br-d,2H), 7.31(d,J=8.2Hz,2H), 7.56(d,J=5.2Hz,1H), 8.01(s,1H), 8.04(d,J=8.2Hz,2H), 8.07(d,J=5.2Hz,1H), 10.79(br-s,1H).

MS(FAB) m/z 382(M+H)$^+$.

Example 437 Synthesis of 7-(4-ethylpiperazin-1-yl)-5-[3-chloro-4-(2-hydroxyethoxy)phenyl]thieno[2,3-c]pyridine



In the same manner as in Example 161-2, 2-acetoxy-1-

[2-chloro-4-(tributylstannyl)phenoxy]ethane (0.58 g) was obtained as a colorless oil from 2-acetoxy-1-(4-bromo-2-chlorophenoxy)ethane (1.32 g) and bis(tributyltin) (2.3 ml).

The resulting compound and 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (0.19 g) were reacted in the same manner as in Example 300-4, to give a reaction solution containing 7-(4-ethylpiperazin-1-yl)-5-[4-(2-acetoxyethoxy)-3-chlorophenyl]thieno[2,3-c]pyridine. Ethyl acetate and 2N hydrochloric acid were added to the reaction solution, and the resulting insoluble matters were filtered off. The aqueous layer was separated, while the organic layer was extracted with 2N hydrochloric acid. The resulting aqueous layers were combined and washed with ethyl acetate twice. The pH of the resulting solution was adjusted to pH 10 by adding a 8N aqueous solution of sodium hydroxide, and then the solution was extracted with ethyl acetate twice. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated. Methanol (6 ml) was added to the resulting residue and dissolved, followed by the addition of a 8N aqueous solution of sodium hydroxide (0.75 ml). The resulting mixture was left as it was at room temperature for 45 min, and then the solvent was evaporated. Water was added to the resulting residue, and then the mixture was extracted with ethyl acetate thrice. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated. The resulting residue was purified by NH silica gel column chromatography (ethyl

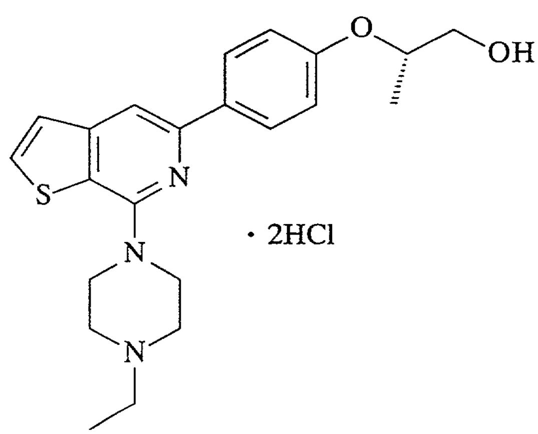
acetate/n-hexane system), to give the title compound (0.03 g) as a colorless viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.52(q,J=7.2Hz,2H), 2.69(t,J=4.8Hz,4H), 3.85(t,J=4.8Hz,4H), 4.30(t,J=4.8Hz,2H), 4.50(t,J=4.8Hz,2H), 7.01(d,J=8.4Hz,1H), 7.34(d,J=5.6Hz,1H), 7.57(d,J=5.6Hz,1H), 7.60(s,1H), 7.95(dd,J=2.4,8.4Hz,1H), 8.13(d,J=2.4Hz,1H).

MS(FAB) m/z 418, 420$(M+H)^+$.

<u>Example 438 Synthesis of 7-(4-ethylpiperazin-1-yl)-5-[4-(1-methyl-2-hydroxyethoxy)phenyl]thieno[2,3-c]pyridine dihydrochloride</u>



In the same manner as in Example 161-2, 1-(S)-acetoxy-2-[4-(tributylstannyl)phenoxy]propane (1.12 g) was obtained as a colorless oil from 1-(S)-acetoxy-2-(4-bromophenoxy)propane (1.61 g) and bis(tributyltin) (3.0 ml).

The resulting compound and 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (0.19 g) were reacted in the same manner as in Example 300-4, to give a reaction solution

containing 7-(4-ethylpiperazin-1-yl)-5-[4-(S)-(1-acetoxypropan-2-yl)oxyphenyl]thieno[2,3-c]pyridine. Ethyl acetate and 2N hydrochloric acid were added to the reaction solution and dissolved, and the resulting insoluble matters were filtered off. The aqueous layer was separated, while the organic layer was extracted with 2N hydrochloric acid. The resulting aqueous layers were combined and washed with ethyl acetate twice. The pH of the resulting solution was adjusted to pH 10 by adding a 8N aqueous solution of sodium hydroxide thereto, and the solution was extracted with ethyl acetate twice. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated. To the resulting residue was added methanol (6 ml) and dissolved, followed by the addition of a 8N aqueous solution of sodium hydroxide (1.48 ml). The resulting solution was left as it was at room temperature for 2 hr, and then the solvent was evaporated. Water was added to the residue, and the mixture was extracted with ethyl acetate thrice. Then, it was washed with brine, dried and the solvent was evaporated. The resulting residue was purified by NH silica gel column chromatography (ethyl acetate/n-hexane system), to give 0.15 g of the free compound of the title compound as a colorless viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 1.31(d,J=6.4Hz,3H), 2.37(br-s,1H), 2.52(q,J=7.2Hz,2H), 2.69(t,J=5.0Hz,4H), 3.84-3.88(m,5H), 4.01(dd,J=3.2,9.2Hz,1H),

4.19-4.28(m,1H), 7.00(d,J=8.8Hz,2H), 7.33(d,J=5.4Hz,1H), 7.55(d,J=5.4Hz,1H), 7.62(s,1H), 8.05(d,J=8.8Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a yellow powder.

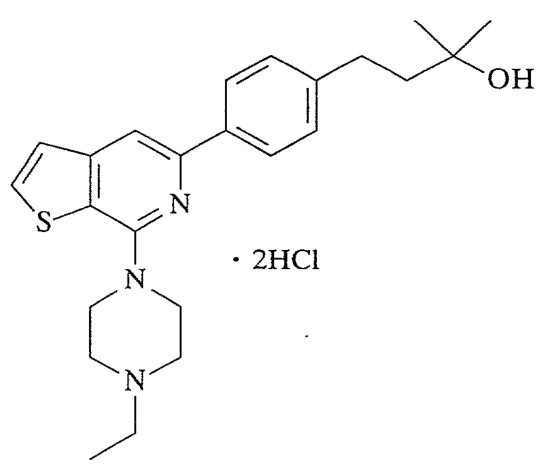
Hydrochloride:

m.p.; 126-127°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.18(d,J=6.4Hz,3H), 1.31(t,J=7.2Hz,3H), 3.16-3.24(m,2H), 3.55(br-t,2H), 3.64(br-d,2H), 3.84(dd,J=5.2,9.6Hz,1H), 3.89(dd,J=6.0,9.6Hz,1H), 3.95-4.01(m,1H), 4.42(br-d,2H), 7.05(d,J=8.8Hz,2H), 7.54(d,J=5.6Hz,1H), 7.97(s,1H), 8.05-8.09(m,3H), 10.91(br-s,1H).

MS(FAB) m/z 398(M+H)$^+$.

Example 439 Synthesis of 7-(4-ethylpiperazin-1-yl)-5-[4-(3-hydroxy-3-methylbutyl)phenyl]thieno[2,3-c]pyridine dihydrochloride



In the same manner as in Example 161-2, 4-[4-(tributylstannyl)phenyl]butan-2-one (1.61 g) was obtained as a colorless oil from 4-(4-bromophenyl)butan-2-one (1.36 g) and bis(tributyltin) (3.0 ml).

The resulting compound and 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (0.33 g) were reacted in the same manner as in Example 300-4, to give 7-(4-ethylpiperazin-1-yl)-5-[4-(3-oxobutyl)phenyl]thieno[2,3-c]pyridine (0.23 g).

The resulting 7-(4-ethylpiperazin-1-yl)-5-[4-(3-oxobutyl)phenyl]thieno[2,3-c]pyridine (0.23 g) was dissolved in tetrahydrofuran (10 ml), and the resulting mixture was stirred under ice-cooling. To the resulting mixture was added 3.0M methylmagnesium bromide/ether solution (0.39 ml), and the mixture was further stirred for 3 hr. Then, 3.0M methylmagnesium bromide/ether solution (0.39 ml) was further added thereto, and the mixture was further stirred for 4.5 hr. Then, an aqueous solution of saturated ammonium chloride and ethyl acetate were added to the mixture, and the mixture was stirred. The organic layer was separated, and then it was washed with brine and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by NH silica gel column chromatography (ethyl acetate/n-hexane system), to give 0.10 g of the free compound of the title compound as a colorless viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 1.31(s,6H),

1.81-1.86(m,2H), 2.52(q,J=7.2Hz,2H), 2.69(t,J=5.0Hz,4H), 2.74-2.78(m,2H), 3.85(t,J=5.0Hz,4H), 7.29(d,J=8.4Hz,2H), 7.33(d,J=5.4Hz,1H), 7.55(d,J=5.4Hz,1H), 7.65(s,1H), 8.02(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a yellow powder.

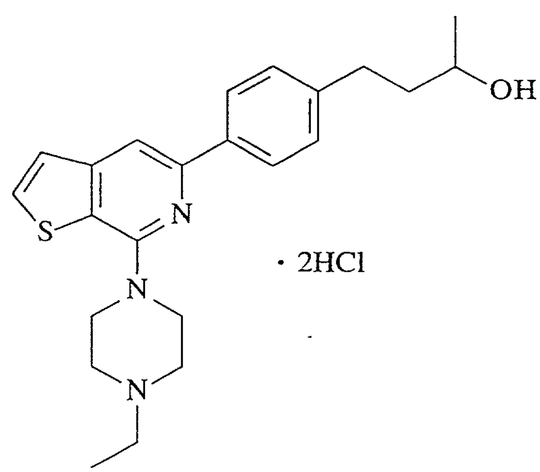
Hydrochloride:

m.p.; 122-123.5°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.17(s,6H), 1.32(t,J=7.2Hz,3H), 1.65-1.70(m,2H), 2.65-2.70(m,2H), 3.15-3.24(m,4H), 3.57-3.65(m,4H), 4.42(br-d,2H), 7.31(d,J=8.0Hz,2H), 7.56(d,J=5.4Hz,1H), 8.00(s,1H), 8.04(d,J=8.0Hz,2H), 8.08(d,J=5.4Hz,1H), 11.28(br-s,1H).

MS(FAB) m/z 410(M+H)$^+$.

<u>Example 440</u> <u>Synthesis of 7-(4-ethylpiperazin-1-yl)-5-[4-(3-hydroxybutyl)phenyl]thieno[2,3-c]pyridine dihydrochloride</u>



In the same manner as in Example 161-2, 4-[4-(tributylstannyl)phenyl]butan-2-one (1.59 g) was obtained as a colorless oil from 4-(4-bromophenyl)butan-2-one (1.29 g) and bis(tributyltin) (2.9 ml).

The resulting compound and 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (0.22 g) were reacted in the same manner as in Example 300-4, to give 7-(4-ethylpiperazin-1-yl)-5-[4-(3-oxobutyl)phenyl]thieno[2,3-c]pyridine.

The resulting 7-(4-ethylpiperazin-1-yl)-5-[4-(3-oxobutyl)phenyl]thieno[2,3-c]pyridine was dissolved in tetrahydrofuran (5 ml). The resulting solution was added to a suspension of lithium aluminum hydride (0.04 g) in tetrahydrofuran (1 ml) under ice-cooling, and the mixture was further stirred for 15 min. Water (40 ml), a 5N aqueous solution of sodium hydroxide (40 ml) and water (120 ml) were sequentially added to the reaction solution. Then, the resulting mixture was diluted with ethyl acetate, and the resulting precipitates were filtered off. The solvent was evaporated, and the resulting residue was purified by NH silica gel column chromatography (ethyl acetate/n-hexane system), to give 0.18 g of the free compound of the title compound as a colorless viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 1.25(d,J=3.2Hz,3H), 1.78-1.85(m,2H), 2.52(q,J=7.2Hz,2H), 2.69(t,J=5.0Hz,4H), 2.65-2.85(m,2H), 3.84-3.89(m,5H),

7.29(d,J=8.4Hz,2H), 7.34(d,J=5.4Hz,1H), 7.56(d,J=5.4Hz,1H), a7.66(s,1H), 8.02(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a yellow powder.

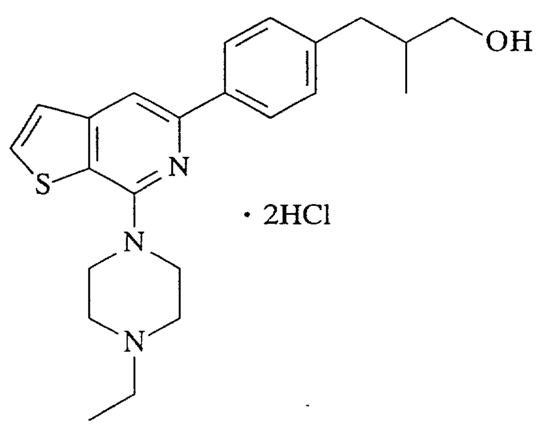
Hydrochloride:

m.p.; 110.5-112°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.10(d,J=6.0Hz,3H), 1.31(t,J=7.2Hz,3H), 1.62-1.68(m,2H), 2.60-2.76(m,2H), 3.15-3.23(m,4H), 3.57-3.65(m,4H), 4.42(br-d,2H), 7.31(d,J=8.4Hz,2H), 7.56(d,J=5.4Hz,1H), 8.00(s,1H), 8.04(d,J=8.0Hz,2H), 8.08(d,J=5.4Hz,1H), 11.26(br-s,1H).

MS(FAB) m/z 396(M+H)$^+$.

<u>Example 441 Synthesis of 7-(4-ethylpiperazin-1-yl)-5-[4-(3-hydroxy-2-methylpropyl)phenyl]thieno[2,3-c]pyridine dihydrochloride</u>



In the same manner as in Example 161-2, methyl 2-methyl-3-[4-(tributylstannyl)phenyl]propionate (1.52 g) was

obtained as a colorless oil from methyl 3-(4-bromophenyl)-2-methylpropionate (1.36 g) and bis(tributyltin) (2.7 ml).

The resulting compound and 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (0.22 g) were reacted in the same manner as in Example 300-4, to give 7-(4-ethylpiperazin-1-yl)-5-[4-(2-methoxycarbonylpropyl)phenyl]thieno[2,3-c]pyridine.

The resulting 7-(4-ethylpiperazin-1-yl)-5-[4-(2-methoxycarbonylpropyl)phenyl]thieno[2,3-c]pyridine was dissolved in tetrahydrofuran (5 ml). The resulting solution was added to a suspension of lithium aluminum hydride (0.05 g) in tetrahydrofuran (0.5 ml) under ice-cooling, and the mixture was further stirred for 20 min. Water (50 ml), a 5N aqueous solution of sodium hydroxide (50 ml) and water (150 ml) were sequentially added thereto. The resulting mixture was then diluted with ethyl acetate, and the resulting precipitates were filtered off. The solvent was evaporated, and the resulting residue was purified by NH silica gel column chromatography (ethyl acetate/n-hexane system), to give 0.17 g of the free compound of the titled compound as a colorless viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.94(d,J=6.8Hz,3H), 1.16(t,J=7.2Hz,3H), 1.93-2.02(m,1H), 2.46(dd,J=8.2,13.6Hz,1H), 2.51(q,J=7.2Hz,2H), 2.68(t,J=5.0Hz,4H), 2.81(dd,J=6.0,13.6Hz,1H), 3.49(dd,J=6.0,10.4Hz,1H), 3.55(dd,J=6.0,10.4Hz,1H),

3.85(t,J=5.0Hz,4H), 7.25(d,J=8.4Hz,2H), 7.32(d,J=5.6Hz,1H), 7.54(d,J=5.6Hz,1H), 7.65(s,1H), 8.01(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a yellow powder.

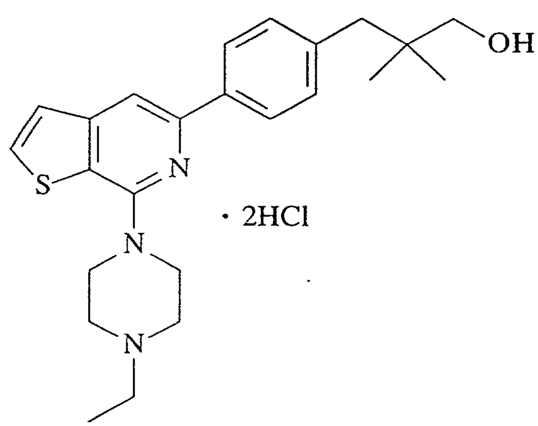
Hydrochloride:

m.p.; 108-110°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.82(d,J=6.8Hz,3H), 1.32(t,J=7.2Hz,3H), 1.79-1.88(m,1H), 2.35(dd,J=8.2,13.2Hz,1H), 2.78(dd,J=5.6,13.2Hz,1H), 3.15-3.24(m,4H), 3.26(dd,J=6.2,10.4Hz,1H), 3.31(dd,J=6.0,10.4Hz,1H), 3.62(br-t,4H), 4.42(br-d,2H), 7.29(d,J=8.0Hz,2H), 7.57(d,J=5.4Hz,1H), 8.01(s,1H), 8.05(d,J=8.4Hz,1H), 8.08(d,J=5.4Hz,1H), 11.28(br-s,1H).

MS(FAB) m/z 396(M+H)$^+$.

Example 442 Synthesis of 7-(4-ethylpiperazin-1-yl)-5-[4-(3-hydroxy-2,2-dimethylpropyl)phenyl]thieno[2,3-c]pyridine dihydrochloride



In the same manner as in Example 161-2, methyl 2,2-dimethyl-3-[4-(tributylstannyl)phenyl]propionate (1.51 g) was obtained as a colorless oil from methyl 3-(4-bromophenyl)-2,2-dimethylpropionate (1.29 g) and bis(tributyltin) (2.4 ml).

The resulting compound and 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (0.23 g) were reacted in the same manner as in Example 300-4, to give 7-(4-ethylpiperazin-1-yl)-5-[4-(2-methoxycarbonyl-2-methylpropyl)phenyl]thieno[2,3-c]pyridine.

The resulting 7-(4-ethylpiperazin-1-yl)-5-[4-(2-methoxycarbonylpropyl)phenyl]thieno[2,3-c]pyridine was dissolved in tetrahydrofuran (5 ml). The resulting solution was added to a suspension of lithium aluminum hydride (0.05 g) in tetrahydrofuran (1 ml) under ice-cooling, and the mixture was further stirred for 30 min. Water (50 ml), a 5N aqueous solution of sodium hydroxide (50 ml) and water (150 ml) were sequentially added thereto. The resulting mixture was then diluted with ethyl acetate, and the resulting precipitates were filtered off. The solvent was evaporated, and the resulting residue was purified by NH silica gel column chromatography (ethyl acetate/n-hexane system), to give 0.22 g of the title compound as a colorless viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.91(s,6H), 1.16(t,J=7.2Hz,3H), 1.93(br-s,1H), 2.51(q,J=7.2Hz,2H), 2.62(s,2H),

2.68(t,J=5.0Hz,4H), 3.34(s,2H), 3.85(t,J=5.0Hz,4H), 7.24(d,J=8.2Hz,2H), 7.32(d,J=5.4Hz,1H), 7.54(d,J=5.4Hz,1H), 7.66(s,1H), 8.01(d,J=8.2Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a yellow powder.

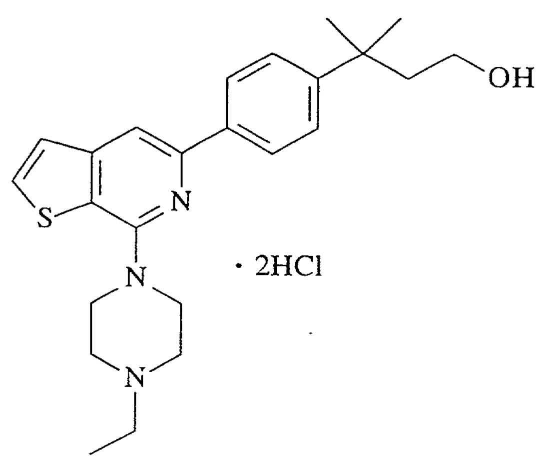
Hydrochloride:

m.p.; 113-114°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.81(s,6H), 1.32(t,J=7.2Hz,3H), 1.92(s,2H), 3.12(s,2H), 3.15-3.24(m,4H), 3.62-3.68(m,4H), 4.43(br-d,2H), 7.27(d,J=8.2Hz,2H), 7.57(d,J=5.4Hz,1H), 8.02(s,1H), 8.04(d,J=8.2Hz,2H), 8.09(d,J=5.4Hz,1H), 11.49(br-s,1H).

MS(FAB) m/z 410(M+H)$^+$.

Example 443 Synthesis of 7-(4-ethylpiperazin-1-yl)-5-[4-(3-hydroxy-1,1-dimethylpropyl)phenyl]thieno[2,3-c]pyridine dihydrochloride



In the same manner as in Example 161-2, 3-acetoxy-1,1-dimethyl-1-[4-(tributylstannyl)phenoxy]propane (1.36 g) was obtained as a colorless oil from 1-acetoxy-3-(4-bromophenoxy)-3-methylbutane (1.34 g) and bis(tributyltin) (2.4 ml).

The resulting compound and 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (0.20 g) were reacted in the same manner as in Example 300-4, to give a reaction solution containing 7-(4-ethylpiperazin-1-yl)-5-[4-(3-acetoxy-1,1-dimethylpropyl)phenyl]thieno[2,3-c]pyridine. Ethyl acetate and 2N hydrochloric acid were added to the reaction solution, and the resulting insoluble matters were filtered off. The aqueous layer was separated, while the organic layer was extracted with 2N hydrochloric acid. The aqueous layers were combined and washed with ethyl acetate twice. The pH of the resulting solution was adjusted to pH 10 by adding a 8N aqueous solution of sodium hydroxide thereto, and the solution was extracted with ethyl acetate twice. The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated. Methanol (10 ml) was added to the resulting residue and dissolved, followed by the addition of a 8N aqueous solution of sodium hydroxide (0.75 ml). The resulting solution was left as it was at room temperature for 2 hr, and then the solvent was evaporated. Water was added to the resulting residue, and then the mixture was extracted with ethyl acetate thrice. The extract was washed with brine, dried over magnesium sulfate,

and the solvent was evaporated. The resulting residue was purified by NH silica gel column chromatography (ethyl acetate/n-hexane system), to give 0.16 g of the free compound of the title compound as a colorless viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.15(t,J=7.2Hz,3H), 1.38(s,6H), 1.98(t,J=7.6Hz,2H), 2.50(q,J=7.2Hz,2H), 2.67(t,J=5.0Hz,2H), 3.51(t,J=7.6Hz,2H), 3.84(t,J=5.0Hz,4H), 7.32(d,J=5.4Hz,1H), 7.43(d,J=8.4Hz,2H), 7.53(d,J=5.4Hz,1H), 7.64(s,1H), 8.03(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/IPE, to give the title compound as a yellow powder.

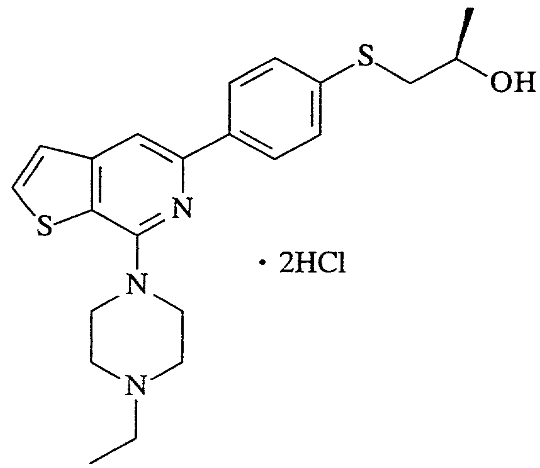
Hydrochloride:

m.p.; 125.5-127.5°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.30(t,J=7.2Hz,3H), 1.32(s,6H), 1.85(t,J=7.8Hz,2H), 3.15-3.25(m,2H), 3.57(br-t,2H), 3.64(br-d,2H), 4.44(br-d,2H), 7.46(d,J=8.4Hz,2H), 7.57(d,J=5.4Hz,1H), 8.01(s,1H), 8.06(d,J=8.4Hz,2H), 8.08(d,J=5.4Hz,1H), 10.89(br-s,1H).

MS(FAB) m/z 410$(M+H)^+$.

Example 444 Synthesis of 7-(4-ethylpiperazin-1-yl)-5-[4-(2-hydroxypropylthio)phenyl]thieno[2,3-c]pyridine dihydrochloride



In the same manner as in Example 161-2, (R)-2-acetoxy-1-[4-(tributylstannyl)phenylthio]propane (0.79 g) was obtained as a colorless oil from (R)-2-acetoxy-1-(4-bromophenylthio)propane (1.14 g) and bis(tributyltin) (2.2 ml).

The resulting compound and 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (0.20 g) were reacted in the same manner as in Example 300-4, to give a reaction solution containing 7-(4-ethylpiperazin-1-yl)-5-[4-(R)-2-acetoxypropylthio]phenyl]thieno[2,3-c]pyridine. Ethyl acetate and 2N hydrochloric acid were added to the reaction solution, and the resulting insoluble matters were filtered off. The aqueous layer was separated, while the organic layer was extracted with 2N hydrochloric acid. The aqueous layers were combined and washed with ethyl acetate twice. The pH of the resulting solution was adjusted to pH 10 by adding a 8N aqueous solution of sodium hydroxide thereto, and the resulting solution was extracted with ethyl acetate twice. The extract

was washed with brine, dried over magnesium sulfate, and the solvent was evaporated. Methanol (10 ml) was added to the resulting residue and dissolved, followed by the addition of a 8N aqueous solution of sodium hydroxide (0.74 ml). The resulting solution was left as it was at room temperature for 2 hr, and then the solvent was evaporated. Water was added to the resulting residue, and then the resulting mixture was extracted with ethyl acetate thrice. The resulting extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated. The resulting residue was purified by NH silica gel column chromatography (ethyl acetate/n-hexane system), to give 0.14 g of the free compound of the title compound as a colorless viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 1.29(d,J=6.4Hz,3H), 2.51(q,J=7.2Hz,2H), 2.68(t,J=5.0Hz,4H), 2.89(dd,J=8.6,13.6Hz,1H), 3.15(dd,J=3.6,13.6Hz,1H), 3.85(t,J=5.0Hz,4H), 3.86-3.94(m,1H), 7.33(d,J=5.4Hz,1H), 7.46(d,J=8.4Hz,2H), 7.56(d,J=5.4Hz,1H), 7.64(s,1H), 8.03(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/IPE, to give the title compound as a yellow powder.

Hydrochloride:

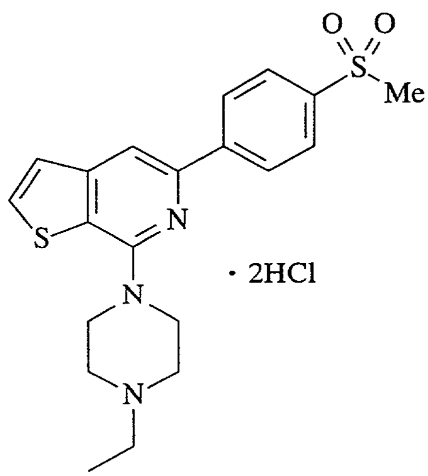
m.p.; 98.5-99.5°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.19(d,J=6.0Hz,3H),

1.30(t,J=7.2Hz,3H), 2.97(dd,J=6.2,13.2Hz,1H), 3.08(dd,J=6.0,13.2Hz,1H), 3.16-3.23(m,4H), 3.56(br-t,2H), 3.64(br-d,2H), 4.43(br-d,2H), 7.43(d,J=8.8Hz,2H), 7.56(d,J=5.2Hz,1H), 8.03(s,1H), 8.06-8.09(m,3H), 10.87(br-s,1H).

MS(ESI) m/z 414$(M+H)^+$.

Example 445 Synthesis of 7-(4-ethylpiperazin-1-yl)-5-(4-methanesulfonylphenyl)thieno[2,3-c]pyridine dihydrochloride



In the same manner as in Example 161-2, 1-methanesulfonyl-4-(tributylstannyl)benzene (0.58 g) was obtained as a colorless oil from 4-methanesulfonylbromobenzene (1.50 g) and bis(tributyltin) (3.6 ml).

The resulting compound and 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (0.18 g) were reacted in the same manner as in Example 300-4, to give a reaction solution containing 7-(4-ethylpiperazin-1-yl)-5-(4-methanesulfonylphenyl)thieno[2,3-c]pyridine. Ethyl acetate and 2N hydrochloric acid were added to the reaction solution,

and the resulting insoluble matters were filtered off. The aqueous layer was separated, while the organic layer was extracted with 2N hydrochloric acid. The aqueous layers were combined and washed with ethyl acetate. The pH of the resulting solution was adjusted to pH 10 by adding a 8N aqueous solution of sodium hydroxide thereto, and the resulting solution was extracted with ethyl acetate twice. After washing with brine and drying over magnesium sulfate, the solvent was evaporated. The resulting residue was purified by NH silica gel column chromatography (ethyl acetate/n-hexane system), to give 0.19 g of the free compound of the title compound as a pale brown viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.53(q,J=7.2Hz,2H), 2.71(t,J=5.0Hz,4H), 3.10(s,3H), 3.88(t,J=5.0Hz,4H), 7.40(d,J=5.2Hz,1H), 7.64(d,J=5.2Hz,1H), 7.75(s,1H), 8.02(d,J=8.4Hz,2H), 8.29(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/IPE, to give the title compound as a yellow powder.

Hydrochloride:

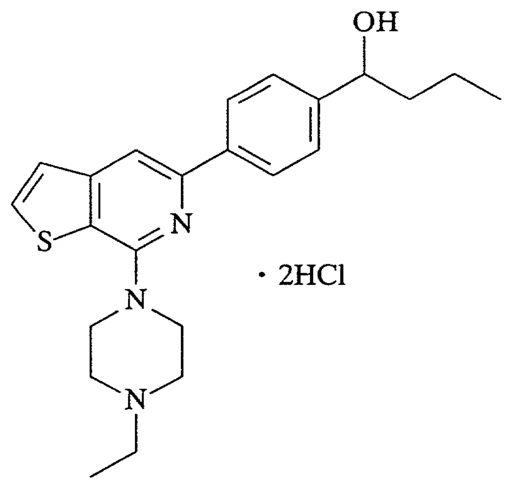
m.p.; 222.5-225°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.30(t,J=7.2Hz,3H), 3.18-3.28(m,4H), 3.28(s,3H), 3.55(br-t,2H), 3.66(br-d,2H), 4.48(br-d,2H), 7.62(d,J=5.4Hz,1H), 8.03(d,J=8.4Hz,2H), 8.15(d,J=5.4Hz,1H), 8.21(s,1H), 8.40(d,J=8.4Hz,2H),

10.59(br-s,1H).

MS(FAB) m/z 402(M+H)$^+$

Example 446 Synthesis of 7-(4-ethylpiperazin-1-yl)-5-[4-(1-hydroxybutyl)phenyl]thieno[2,3-c]pyridine dihydrochloride



In the same manner as in Example 161-2, 1-[4-(tributylstannyl)phenyl]butan-1-one (1.74 g) was obtained as a colorless oil from 1-(4-bromophenyl)butan-1-one (1.91 g) and bis(tributyltin) (4.7 ml).

The resulting compound and 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (0.22 g) were reacted in the same manner as in Example 300-4, to give 7-(4-ethylpiperazin-1-yl)-5-(4-butyrylphenyl)thieno[2,3-c]pyridine (0.17 g).

The resulting 7-(4-ethylpiperazin-1-yl)-5-(4-butyrylphenyl)thieno[2,3-c]pyridine (0.17 g) was dissolved in tetrahydrofuran (6 ml). The resulting solution was added to a suspension of lithium aluminum hydride (0.02 g) in tetrahydrofuran (0.5 ml) under ice-cooling, and the mixture was further stirred for 25 min. To the reaction solution were

sequentially added water (20 ml), a 5N aqueous solution of sodium hydroxide (20 ml) and water (60 ml). The resulting mixture was diluted with ethyl acetate, and then the resulting precipitates were filtered off. The solvent was evaporated, and the resulting residue was purified by NH silica gel column chromatography (ethyl acetate/n-hexane system), to give 0.13 g of the free compound of the title compound as a colorless viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.94(t,J=7.2Hz,3H), 1.15(t,J=7.2Hz,3H), 1.29-1.40(m,1H), 1.40-1.52(m,1H), 1.66-1.75(m,1H), 1.78-1.88(m,1H), 2.42(br-s,1H), 2.49(q,J=7.2Hz,2H), 2.66(t,J=5.0Hz,4H), 3.82(t,J=5.0Hz,4H), 4.71(br-t,1H), 7.32(d,J=5.4Hz,1H), 7.41(d,J=8.2Hz,2H), 7.54(d,J=5.4Hz,1H), 8.06(d,J=8.2Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a yellow powder.

Hydrochloride:

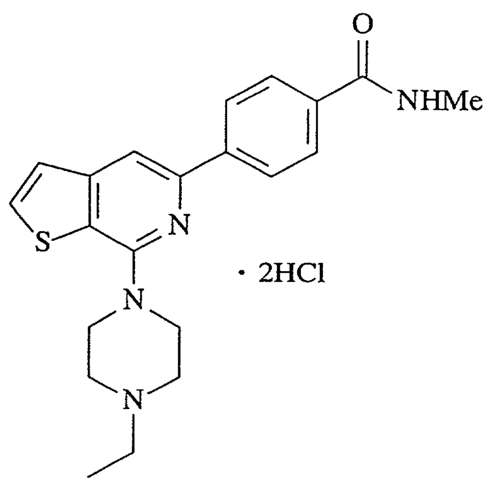
m.p.; 112-114°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.88(t,J=7.4Hz,3H), 1.06(t,J=6.8Hz,3H), 1.23-1.42(m,2H), 1.52-1.69(m,2H), 3.15-3.23(m,4H), 3.58-3.66(m,4H), 4.42(br-d,2H), 4.58(t,J=6.4Hz,1H), 7.43(d,J=8.2Hz,2H), 7.57(d,J=5.6Hz,1H), 8.02(s,1H), 8.08(d,J=8.2Hz,2H), 8.09(d,J=5.6Hz,1H),

11.46(br-s,1H).

MS(FAB) m/z 396$(M+H)^+$.

<u>Example 447 Synthesis of 7-(4-ethylpiperazin-1-yl)-5-[4-(N-methylcarbamoyl)phenyl]thieno[2,3-c]pyridine dihydrochloride</u>



In the same manner as in Example 161-2, N-methyl-4-(tributylstannyl)benzamide (0.90 g) was obtained as a colorless oil from N-methyl-4-bromobenzamide (1.13 g) and bis(tributyltin) (2.9 ml).

The resulting compound and 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (0.19 g) were reacted in the same manner as in Example 300-4, to give 0.16 g of the free compound of the title compound as a colorless viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.15(t,J=7.2Hz,3H), 2.51(q,J=7.2Hz,2H), 3.68(t,J=5.0Hz,4H), 3.03(d,J=4.8Hz,3H), 3.85(t,J=5.0Hz,4H), 6.35(br-q,1H), 7.33(d,J=5.4Hz,1H), 7.57(d,J=5.4Hz,1H), 7.69(s,1H), 7.84(d,J=9.0Hz,2H),

8.14(d,J=9.0Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/IPE, to give the title compound as a yellow powder.

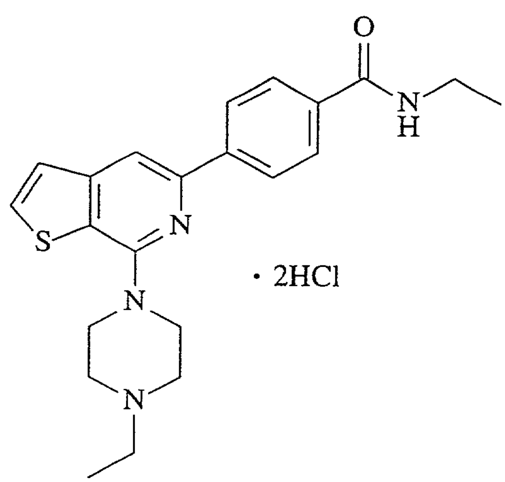
Hydrochloride:

m.p.; 150.5-152°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.30(t,J=7.2Hz,3H), 2.82(d,J=3.6Hz,3H), 3.18-3.26(m,4H), 3.55(br-t,2H), 3.66(br-d,2H), 4.47(br-d,2H), 7.59(d,J=5.4Hz,1H), 7.95(d,J=8.4Hz,1H), 8.11(d,J=5.4Hz,1H), 8.15(s,1H), 8.22(d,J=8.4Hz,2H), 8.53(br-q,1H), 10.65(br-s,1H).

MS(FAB) m/z 381(M+H)$^+$.

Example 448 Synthesis of 7-(4-ethylpiperazin-1-yl)-5-[4-(N-ethylcarbamoyl)phenyl]thieno[2,3-c]pyridine dihydrochloride



In the same manner as in Example 161-2, N-ethyl-4-(tributylstannyl)benzamide (0.84 g) was obtained as a colorless oil from N-ethyl-4-bromobenzamide (1.11 g) and bis(tributyltin) (2.7 ml).

The resulting compound and 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (0.19 g) were reacted in the same manner as in Example 300-4, to give 0.19 g of the free compound of the title compound as a colorless viscous oil.

Free compound:

^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 1.16(t,J=7.2Hz,3H), 1.27(t,J=7.2Hz,3H), 2.51(q,J=7.2Hz,2H), 2.68(t,J=5.0Hz,4H), 3.52(qd,J=5.2,7.2Hz,2H), 3.85(t,J=5.0Hz,4H), 6.26(br-t,1H), 7.34(d,J=5.4Hz,1H), 7.57(d,J=5.4Hz,1H), 7.70(s,1H), 7.84(d,J=8.2Hz,2H), 8.14(d,J=8.2Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/IPE, to give the title compound as a pale yellow powder.

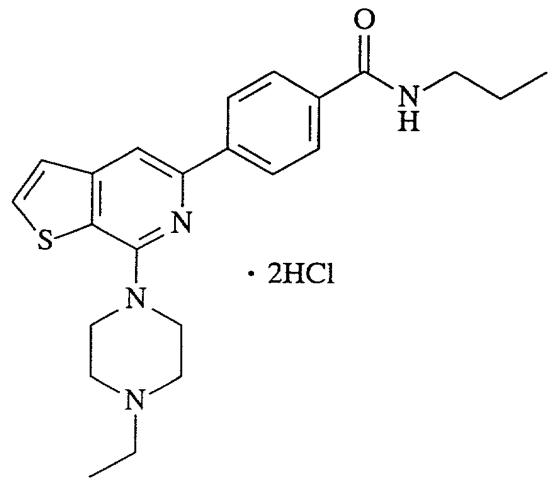
Hydrochloride:

m.p.; 142-143°C

^{1}H-NMR(400MHz,DMSO-d_6); δ(ppm) 1.15(t,J=7.2Hz,3H), 1.31(t,J=7.2Hz,3H), 3.17-3.25(m,4H), 3.29-3.35(m,2H), 3.58(br-t,2H), 3.66(br-d,2H), 4.46(br-d,2H), 7.59(d,J=5.6Hz,1H), 7.96(d,J=8.4Hz,2H), 8.10(d,J=5.6Hz,1H), 8.15(s,1H), 8.22(d,J=8.4Hz,2H), 8.57(t,J=5.4Hz,1H), 10.97(br-s,1H).

MS(FAB) m/z 395$(M+H)^+$.

Example 449 Synthesis of 7-(4-ethylpiperazin-1-yl)-5-[4-(N-propylcarbamoyl)phenyl]thieno[2,3-c]pyridine dihydrochloride



In the same manner as in Example 161-2, N-ethyl-4-(tributylstannyl)benzamide (0.66 g) was obtained as a colorless oil from N-propyl-4-bromobenzamide (1.13 g) and bis(tributyltin) (2.6 ml).

The resulting compound and 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (0.21 g) were reacted in the same manner as in Example 300-4, to give 0.21 g of the free compound of the title compound as a colorless viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.99(t,J=7.4Hz,3H), 1.15(t,J=7.2Hz,3H), 1.66(qt,J=7.2,7.2Hz,2H), 2.50(q,J=7.2Hz,2H), 2.67(t,J=5.0Hz,4H), 3.44(br-q,2H), 3.85(t,J=5.0Hz,4H), 6.36(t,J=5.6Hz,1H), 7.32(d,J=5.4Hz,1H), 7.56(d,J=5.4Hz,2H), 7.68(s,1H), 7.84(d,J=8.8Hz,2H), 8.14(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/IPE, to give the title compound as a pale yellow

powder.

Hydrochloride:

m.p.; 136.5-138°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.91(t,J=7.2Hz,3H),

1.30(t,J=7.2Hz,3H), 1.56(qt,J=7.2,7.2Hz,2H), 3.18-3.27(m,6H),

3.55(br-t,2H), 3.66(br-d,2H), 4.47(br-d,2H),

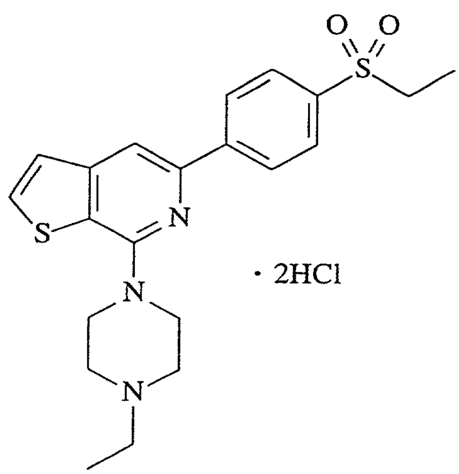
7.60(d,J=5.4Hz,1H), 7.96(d,J=8.4Hz,2H), 8.11(d,J=5.4Hz,1H),

8.14(s,1H), 8.22(d,J=8.4Hz,2H), 8.54(t,J=5.6Hz,1H),

10.63(br-s,1H).

MS(FAB) m/z 409(M+H)$^+$.

Example 450 Synthesis of 7-(4-ethylpiperazin-1-yl)-5-(4-ethanesulfonylphenyl]thieno[2,3-c]pyridine dihydrochloride



In the same manner as in Example 161-2, 4-ethanesulfonyl-4-(tributylstannyl)benzene (0.70 g) was obtained as a colorless oil from 4-ethanesulfonylbromobenzene (1.23 g) and bis(tributyltin) (2.7 ml).

The resulting compound and 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (0.18 g) were reacted in the same

manner as in Example 300-4, to give a reaction solution containing 7-(4-ethylpiperazin-1-yl)-5-(4-ethanesulfonylphenyl)thieno[2,3-c]pyridine. To the resulting reaction solution were added ethyl acetate and 2N hydrochloric acid, and the resulting insoluble matters were filtered off. The aqueous layer was separated, while the organic layer was extracted with 2N hydrochloric acid. The aqueous layers were combined and washed with ethyl acetate. The pH of the resulting solution was adjusted to pH 10 by adding a 8N aqueous solution of sodium hydroxide thereto, and the resulting solution was extracted with ethyl acetate twice. After washing with brine and drying over magnesium sulfate, the solvent was evaporated. The resulting residue was purified by NH silica gel column chromatography (ethyl acetate/n-hexane system), to give 0.20 g of the free compound of the title compound as a pale brown viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.4Hz,3H), 1.31(t,J=7.4Hz,3H), 2.52(q,J=7.4Hz,2H), 2.69(t,J=5.0Hz,4H), 3.15(q,J=7.4Hz,2H), 3.87(t,J=5.0Hz,4H), 7.38(d,J=5.4Hz,1H), 7.61(d,J=5.4Hz,1H), 7.74(s,1H), 7.97(d,J=8.6Hz,2H), 8.28(d,J=8.6Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/IPE, to give the title compound as a yellow powder.

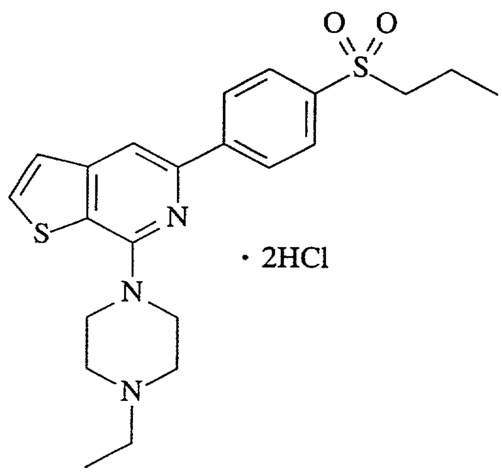
Hydrochloride:

m.p.; 230-232.0°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.14(t,J=7.4Hz,3H), 1.30(t,J=7.4Hz,3H), 3.18-3.26(m,4H), 3.35(q,J=7.4Hz,2H), 3.54(br-t,2H), 3.66(br-d,2H), 4.49(br-d,2H), 7.62(d,J=5.4Hz,1H), 7.99(d,J=8.6Hz,2H), 8.14(d,J=5.4Hz,1H), 8.21(s,1H), 8.41(d,J=8.6Hz,2H), 10.48(br-s,1H).

MS(ESI) m/z 416(M+H)$^+$.

Example 451 Synthesis of 7-(4-ethylpiperazin-1-yl)-5-(4-propanesulfonylphenyl)thieno[2,3-c]pyridine dihydrochloride



In the same manner as in Example 161-2, 1.09 g of 1-propanesulfonyl-4-(tributylstannyl)benzene was obtained as a colorless oil from 4-propanesulfonylbromobenzene (1.40 g) and bis(tributyltin) (3.0 ml).

The resulting compound and 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (0.18 g) were reacted in the same manner as in Example 300-4, to give a reaction solution containing 7-(4-ethylpiperazin-1-yl)-5-(4-propanesulfonylphenyl)thieno[2,3-c]pyridine. To the

resulting reaction solution were added ethyl acetate and 2N hydrochloric acid, and the resulting insoluble matters were filtered off. The aqueous layer was separated, while the organic layer was extracted with 2N hydrochloric acid. The aqueous layers were combined and washed with ethyl acetate. The pH of the solution was adjusted to pH 10 by adding a 8N aqueous sodium hydroxide thereto, and then the solution was extracted with ethyl acetate twice. It was washed with brine, dried over magnesium sulfate, and then the solvent was evaporated. The resulting residue was purified by NH silica gel column chromatography (ethyl acetate/n-hexane system), to give 0.19 g of the free compound of the title compound as a pale brown viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.01(t,J=7.4Hz,3H), 1.16(t,J=7.2Hz,3H), 1.73-1.83(m,2H), 2.52(q,J=7.2Hz,2H), 2.69(t,J=5.0Hz,4H), 3.08-3.12(m,2H), 3.87(t,J=5.0Hz,4H), 7.38(d,J=5.6Hz,1H), 7.62(d,J=5.6Hz,1H), 7.74(s,1H), 7.97(d,J=8.6Hz,2H), 7.27(d,J=8.6Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/IPE, to give the title compound as a yellow powder.

Hydrochloride:

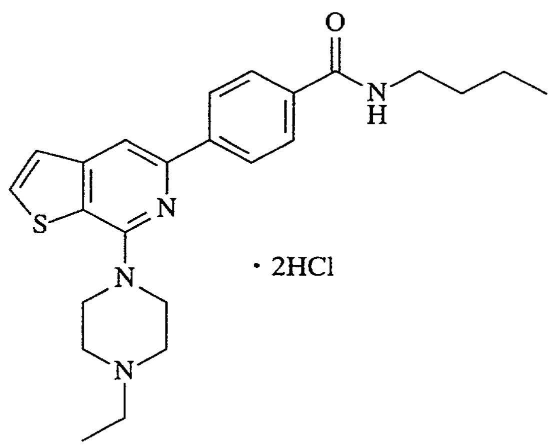
m.p.; 230.5-233.5°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.94(t,J=7.4Hz,3H), 1.30(t,J=7.2Hz,3H), 1.55-1.64(m,2H), 3.17-3.27(m,4H), 3.31-

3.35(m,2H), 3.54(br-t,2H), 3.66(br-d,2H), 3.49(br-d,2H), 7.62(d,J=5.6Hz,1H), 7.99(d,J=8.4Hz,2H), 8.14(d,J=5.6Hz,1H), 8.21(s,1H), 8.40(d,J=8.4Hz,2H), 10.47(br-s,1H).

MS(FAB) m/z 430$(M+H)^+$.

<u>Example 452</u> <u>Synthesis of 7-(4-ethylpiperazin-1-yl)-5-[4-(N-butylcarbamoyl)phenyl]thieno[2,3-c]pyridine dihydrochloride</u>



In the same manner as in Example 161-2, N-butyl-4-(tributylstannyl)benzamide (0.80 g) was obtained as a colorless oil from N-butyl-4-bromobenzamide (1.21 g) and bis(tributyltin) (2.6 ml).

The resulting compound and 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (0.20 g) were reacted in the same manner as in Example 300-4, to give 0.20 g of the free compound of the title compound as colorless crystals.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.96(t,J=7.2Hz,3H), 1.15(t,J=7.2Hz,3H), 1.42(tq,J=7.2,7.2Hz,2H), 1.57-1.65(m,2H), 2.50(q,J=7.2Hz,2H), 2.66(t,J=5.0Hz,4H), 3.44-3.49(m,2H), 3.84(t,J=5.0Hz,4H), 6.38(t,J=5.4Hz,1H), 7.31(d,J=5.6Hz,2H),

7.55(d,J=5.6Hz,1H), 7.67(s,1H), 7.84(d,J=8.4Hz,2H), 8.13(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/IPE, to give the title compound as a pale yellow powder.

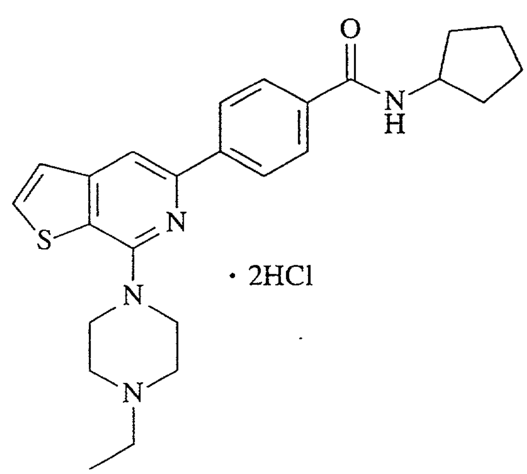
Hydrochloride:

m.p.; 127.5-128°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.92(t,J=7.2Hz,3H), 1.30(t,J=7.2Hz,3H), 1.30-1.40(m,2H), 1.50-1.57(m,2H), 3.18-3.31(m,6H), 3.54(br-t,2H), 3.66(br-d,2H), 4.47(br-d,2H), 7.59(d,J=5.6Hz,1H), 7.96(d,J=8.4Hz,2H), 8.11(d,J=5.6Hz,1H), 8.14(s,1H), 8.22(d,J=8.4Hz,1H), 8.52(t,J=5.8Hz,1H), 10.57(br-s,1H).

MS(FAB) m/z 423(M+H)$^+$.

Example 453 Synthesis of 7-(4-ethylpiperazin-1-yl)-5-[4-(N-cyclopentylcarbamoyl)phenyl]thieno[2,3-c]pyridine dihydrochloride



In the same manner as in Example 161-2, N-cyclopentyl-4-(tributylstannyl)benzamide (0.92 g) was obtained as a colorless oil from N-cyclopentyl-4-bromobenzamide (1.22 g) and bis(tributyltin) (2.5 ml).

7-(1-Ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (0.21 g) was reacted with the resulting compound in the same manner as in Example 300-4, to give 0.21 g of the free compound of the title compound as colorless crystals.

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.15(t,J=7.2Hz,3H), 1.47-1.56(m,2H), 1.60-1.78(m,4H), 2.06-2.14(m,2H), 2.50(q,J=7.2Hz,2H), 2.66(t,J=5.0Hz,4H), 3.84(t,J=5.0Hz,4H), 4.38-4.47(m,1H), 6.26(d,J=7.6Hz,1H), 7.31(d,J=5.2Hz,1H), 7.55(d,J=5.2Hz,1H), 7.68(s,1H), 7.83(d,J=8.4Hz,2H), 8.13(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/IPE, to give the title compound as a pale yellow powder.

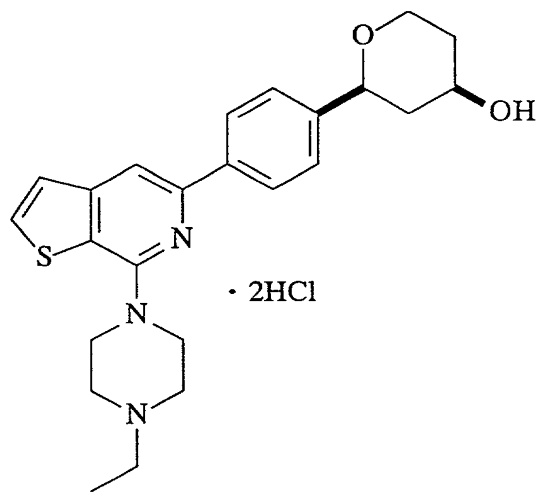
Hydrochloride:

m.p.; 148-149°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.30(t,J=7.2Hz,3H), 1.52-1.62(m,4H), 1.67-1.74(m,2H), 1.86-1.95(m,2H), 3.18-3.26(m,4H), 3.55(br-t,2H), 3.66(br-d,2H), 4.26(br-q,1H), 4.46(br-d,2H), 7.60(d,J=5.4Hz,1H), 7.96(d,J=8.4Hz,2H), 8.11(d,J=5.4Hz,1H), 8.14(s,1H), 8.21(d,J=8.4Hz,2H), 8.35(d,J=7.6Hz,1H), 10.65(br-s,1H).

MS(FAB) m/z 435$(M+H)^+$.

Example 454 Synthesis of 7-(4-Ethylpiperazin-1-yl)-5-[4-(cis-4-hydroxytetrahydropyran-2-yl)phenyl]thieno[2,3-c]pyridine dihydrochloride



In the same manner as in Example 161-2, cis-4-acetoxy-2-[4-(tributylstannyl)phenyl]tetrahydropyran (1.00 g) was obtained as a colorless oil from cis-4-acetoxy–2-(4-bromophenyl)tetrahydropyran (1.20 g) and bis(tributyltin) (2.2 ml).

The resulting compound and 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (0.21 g) were reacted in the same manner as in Example 300-4, to give a reaction solution containing 7-(4-ethylpiperazin-1-yl)-5-[4-(cis-4-acetoxytetrahydropyran-2-yl)phenyl]thieno[2,3-c]pyridine. To the resulting reaction solution were added ethyl acetate and 2N hydrochloric acid, and the resulting insoluble matters were filtered off. The aqueous layer was separated, while the organic phase was extracted with 2N hydrochloric acid. The

aqueous layers were combined and washed with ethyl acetate twice. The pH of the solution was adjusted to pH 10 by adding a 8N aqueous solution of sodium hydroxide thereto, and then the solution was extracted with ethyl acetate twice. After washing with brine and drying over magnesium sulfate, the solvent was evaporated. Methanol (10 ml) was added to the resulting residue and dissolved, followed by the addition of a 5N aqueous solution of sodium hydroxide (1 ml). The resulting solution was left as it was at room temperature for 1 hr, and then the solvent was evaporated. Water was added to the resulting residue, and then the mixture was extracted with ethyl acetate thrice. The extract was washed with brine, dried over magnesium sulfate, and then the solvent was evaporated. The resulting residue was purified by NH silica gel column chromatography (ethyl acetate/n-hexane system), to give 0.20 g of the free compound of the title compound as a colorless amorphous.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.15(t,J=7.2Hz,3H), 1.53-1.70(m,2H), 1.93-1.99(m,1H), 2.15(br-s,1H), 2.16-2.22(m,1H), 2.51(q,J=7.2Hz,2H), 2.68(t,J=5.0Hz,4H), 3.59(dt,J=2.0,12.4Hz,1H), 3.85(t,J=5.0Hz,4H), 3.89-3.97(m,1H), 4.16-4.21(m,1H), 4.34-4.37(m,1H), 7.33(d,J=5.4Hz,1H), 7.42(d,J=8.4Hz,2H), 7.54(d,J=5.4Hz,1H), 7.66(s,1H), 8.06(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated

with ethanol/ether, to give the title compound as a yellow powder.

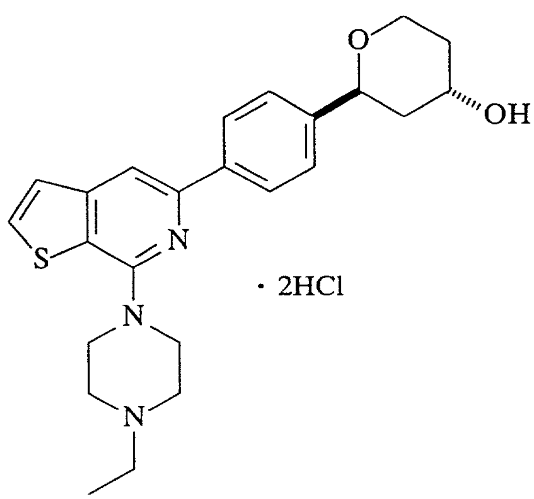
Hydrochloride:

m.p.; 157-159°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.04(d,J=6.0Hz,3H), 1.31(t,J=7.4Hz,3H), 1.38-1.48(m,1H), 1.80-1.86(m,1H), 2.04-2.10(m,1H), 3.16-3.24(m,4H), 3.48-3.66(m,5H), 3.73-3.81(m,1H), 4.02-4.06(m,1H), 4.37(dd,J=1.6,11.2Hz,1H), 4.43(br-d,2H), 7.43(d,J=8.4Hz,2H), 7.57(d,J=5.4Hz,1H), 8.03(s,1H), 8.08(d,J=5.4Hz,1H), 8.09(d,J=8.4Hz,2H), 10.94(br-s,1H).

MS(FAB) m/z 424(M+H)$^{+}$.

Example 455 Synthesis of 7-(4-ethylpiperazin-1-yl)-5-[4-(trans-4-hydroxytetrahydropyran-2-yl)phenyl]thieno[2,3-c]pyridine dihydrochloride



In the same manner as in Example 161-2, trans-4-acetoxy-2-[4-(tributylstannyl)phenyl]tetrahydropyran (1.29 g) was obtained as a colorless oil from trans-4-acetoxy-2-

(4-bromophenyl)tetrahydropyran (1.31 g) and bis(tributyltin) (2.4 ml).

The resulting compound and 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (0.21 g) were reacted in the same manner as in Example 300-4, to give a reaction solution containing 7-(4-ethylpiperazin-1-yl)-5-[4-(trans-4-acetoxytetrahydropyran-2-yl)phenyl]thieno[2,3-c]pyridine. To the resulting reaction solution were added ethyl acetate and 2N hydrochloric acid, and the resulting insoluble matters were filtered off. The aqueous layer was separated, while the organic layer was extracted with 2N hydrochloric acid. The aqueous layers were combined and washed with ethyl acetate twice. The pH of the solution was adjusted to pH 10 by adding a 8N aqueous solution of sodium hydroxide thereto, and then the solution was extracted with ethyl acetate twice. The extract was washed with brine, dried over magnesium sulfate and the solvent was evaporated. Methanol (10 ml) was added to the resulting residue and dissolved, followed by the addition of a 5N aqueous solution of sodium hydroxide solution (1 ml). The resulting solution was left as it was at room temperature for 1 hr, and then the solvent evaporated. Water was added thereto, and then the mixture was extracted with ethyl acetate thrice. The extract was washed with brine, dried over magnesium sulfate, and then the solvent was evaporated. The resulting residue was purified by NH silica gel column chromatography (ethyl acetate/n-hexane system), to give 0.18 g of the free compound of the title compound

as a colorless amorphous.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 1.64(br-d,1H), 1.88-1.91(m,2H), 1.94-2.03(m,1H), 2.06(br-s,1H), 2.51(q,J=7.2Hz,2H), 2.68(t,J=5.0Hz,4H), 3.85(t,J=5.0Hz,4H), 3.95(ddd,J=1.6,5.2,11.6Hz,1H), 4.09(br-dt,1H), 4.31(br-quintet,1H), 4.84-4.92(m,1H), 7.32(d,J=5.4Hz,1H), 7.43(d,J=8.4Hz,2H), 7.54(d,J=5.4Hz,1H), 7.66(s,1H), 7.06(d,J=8.4Hz,2H).

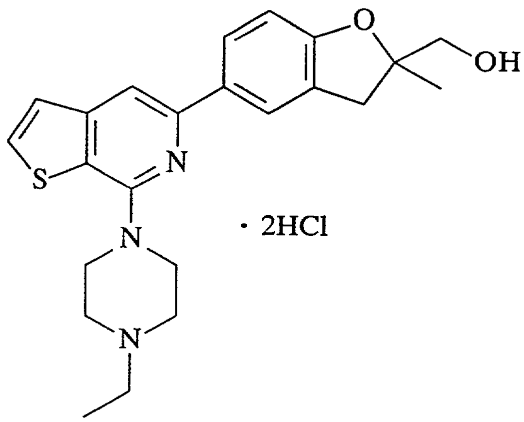
The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a yellow powder.

m.p.; 146-148°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.30(t,J=7.2Hz,3H), 1.54(br-d,1H), 1.68(br-t,1H), 1.74-1.84(m,2H), 1.17-1.24(m,4H), 3.54(br-t,2H), 3.65(br-d,2H), 3.81(br-q,1H), 3.94(br-t,1H), 4.11(br-quintet,1H), 4.43(br-d,2H), 4.77(br-d,1H), 7.41(d,J=8.4Hz,2H), 7.57(d,J=5.6Hz,1H), 8.03(s,1H), 8.08(d,J=5.6Hz,1H), 8.09(d,J=8.4Hz,2H), 10.71(br-s,1H).

MS(FAB) m/z 424$(M+H)^+$.

Example 456 Synthesis of 7-(4-Ethylpiperazin-1-yl)-5-[4-(trans-4-hydroxytetrahydropyran-2-yl)phenyl]thieno[2,3-c]pyridine dihydrochloride



In the same manner as in Example 161-2, 1.10 g of 2-ethoxycarbonyl-2,3-dihydro-2-methyl-5-(tributylstannyl)benzofuran was obtained as a colorless oil from 5-bromo-2-ethoxycarbonyl-2,3-dihydro-2-methylbenzofuran (1.34 g) and bis(tributyltin) (2.6 ml).

The resulting compound and 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (0.29 g) were reacted in the same manner as in Example 300-4, to give 7-(4-ethylpiperazin-1-yl)-5-(2-ethoxycarbonyl-2,3-didhydro-2-methylbenzofuran-5-yl)thieno[2,3-c]pyridine.

The resulting 7-(4-ethylpiperazin-1-yl)-5-(2-ethoxycarbonyl-2,3-dihydro-2-methylbenzofuran-5-yl)thieno[2,3-c]pyridine was dissolved in tetrahydrofuran (10 ml). The resulting solution was added to a suspension of lithium aluminum hydride (0.06 g) in tetrahydrofuran (1 ml) under cooling on ice, and further stirred for 15 min. To the resulting reaction solution were sequentially added water (60 ml), a 5N aqueous solution of sodium hydroxide (60 ml) and water (180 ml). The resulting mixture was diluted with ethyl acetate,

and then the resulting precipitates were filtered off. The solvent was evaporate, and the resulting residue was purified by NH silica gel column chromatography (ethyl acetate/n-hexane system), to give 0.20 g of the free compound of the title compound as a colorless viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.15(t,J=7.2Hz,3H), 1.46(s,3H), 2.50(q,J=7.2Hz,2H), 2.61(br-s,1H), 2.67(t,J=5.0Hz,4H), 2.96(d,J=15.6Hz,1H), 3.31(d,J=15.6Hz,1H), 3.64(d,J=11.6Hz,1H), 3.69(d,J=11.6Hz,1H), 3.82(t,J=5.0Hz,4H), 6.80(d,J=8.4Hz,1H), 7.28(d,J=5.4Hz,1H), 7.51(d,J=5.4Hz,1H), 7.55(s,1H), 7.84(dd,J=1.4,8.4Hz,1H), 7.90(d,J=1.4Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a yellow powder.

Hydrochloride:

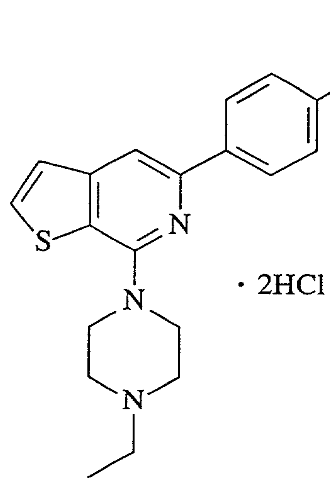
m.p.; 138-140°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.32(t,J=7.2Hz,3H), 1.38(s,3H), 2.91(d,J=15.8Hz,1H), 3.15-3.2(m,4H), 3.30(d,J=15.8Hz,1H), 3.45(d,J=7.0Hz,1H), 3.49(d,J=7.0Hz,1H), 3.55-3.65(m,4H), 4.39(br-d,2H), 6.79(d,J=8.6Hz,1H), 7.52(d,J=5.6Hz,1H), 7.88(dd,J=1.6,8.6Hz,1H), 7.91(s,1H), 7.95(br-s,1H), 8.05(d,J=5.6Hz,1H), 11.25(br-s,1H).

MS(FAB) m/z 410$(M+H)^+$.

Example 457 Synthesis of 7-(4-Ethylpiperazin-1-yl)-5-[4-

(cyclohexylhydroxymethyl)phenyl]thieno[2,3-c]pyridine dihydrochloride



In the same manner as in Example 161-2, 1.39 g of 4-(cyclohexylacetoxymethyl)-1-(tributylstannyl)benzene was obtained as a colorless oil from 4-(cyclohexylacetoxymethyl)bromobenzene (1.36 g) and bis(tributyltin) (2.1 ml).

The resulting compound and 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (0.20 g) were reacted in the same manner as in Example 300-4, to give a reaction solution containing 7-(4-ethylpiperazin-1-yl)-5-[4-(cyclohexylacetoxymethyl)phenyl]thieno[2,3-c]pyridine. To the resulting reaction solution were added ethyl acetate and 2N hydrochloric acid, and then the resulting insoluble matters were filtered off. The aqueous layer was separated, while the organic phase was extracted with 2N hydrochloric acid. The resulting aqueous layers were combined and washed twice with ethyl acetate. The pH of the resulting solution was adjusted

to pH 10 by adding 8N sodium hydroxide thereto, and then the solution was extracted with ethyl acetate twice. After washing with brine and drying over magnesium sulfate, the solvent was evaporated. Methanol (10 ml) was added to the resulting residue, dissolved, and then a 5N aqueous solution of sodium hydroxide (1 ml) was added thereto. The resulting solution was left as it was at room temperature for 1 hr, and then the solvent was evaporated. Water was added thereto, and then the mixture was extracted with ethyl acetate thrice. After washing with brine and drying over magnesium sulfate, the solvent was evaporated. The resulting residue was purified by NH silica gel column chromatography (ethyl acetate/n-hexane system), to give 0.12 g of the free compound of the title compound as a colorless amorphous.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.91-1.28(m,3H), 1.16(t,J=7.2Hz,3H), 1.45(br-d,1H), 1.45(br-d,1H), 1.61-1.69(m,3H), 1.77(br-d,1H), 2.02(br-d,1H), 2.23(br-s,1H), 2.50(q,J=7.2Hz,2H), 2.66(t,J=5.0Hz,4H), 3.83(t,J=7.2Hz,4H), 4.41(d,J=7.2Hz,1H), 7.32(d,J=5.6Hz,1H), 7.37(d,J=8.4Hz,2H), 7.54(d,J=5.6Hz,1H), 7.64(s,1H), 8.05(d,J=8.4Hz,2H).

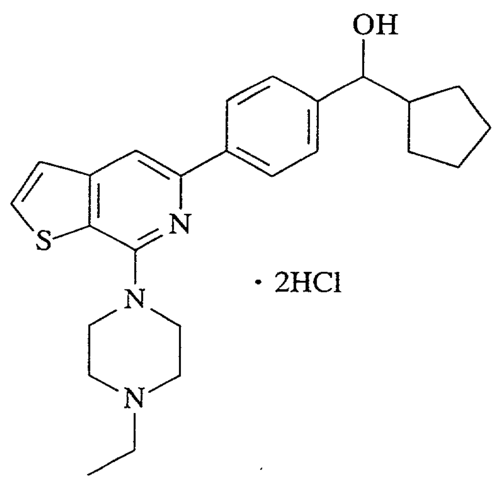
The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a yellow powder.

m.p.; 127.5-129°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 0.92-1.88(m,4H), 1.32(t,J=7.2Hz,3H), 1.38(br-d,1H), 1.46-1.70(m,4H), 1.85(br-d,1H), 3.15-3.24(m,4H), 3.57-3.66(m,5H), 4.30(d,J=6.4Hz,1H), 4.43(br-d,2H), 7.38(d,J=8.4Hz,2H), 7.57(d,J=5.6Hz,1H), 8.02(s,1H), 8.06-8.09(m,3H), 11.41(br-s,1H).

MS(FAB) m/z 436(M+H)$^+$.

Example 458 Synthesis of 7-(4-ethylpiperazin-1-yl)-5-[4-(cyclopentylhydroxymethyl)phenyl]thieno[2,3-c]pyridine dihydrochloride



In the same manner as in Example 161-2, 1.21 g of (4-tributylstannylphenyl)cyclopentyl ketone was obtained as a colorless oil from (4-bromophenyl)cyclopentyl ketone (1.57 g) and bis(tributyltin) (3.1 ml).

The resulting compound and 7-(1-ethylpiperazin-4-yl)-5-bromothieno[2,3-c]pyridine (0.22 g) were reacted in the same manner as in Example 300-4, to give 7-(4-ethylpiperazin-1-yl)-5-[4-(cyclopentylcarbonyl)phenyl]thieno[2,3-c]pyridine.

The resulting 7-(4-ethylpiperazin-1-yl)-5-[4-(cyclopentylcarbonyl)phenyl]thieno[2,3-c]pyridine was dissolved in tetrahydrofuran (5 ml). The resulting solution was added to a suspension of lithium aluminum hydride (0.06 g) in tetrahydrofuran (1 ml) under ice-cooling, and the resulting mixture was further stirred for 10 min. To the resulting reaction solution were sequentially added water (60 ml), a 5N aqueous solution of sodium hydroxide (60 ml) and water (180 ml). The resulting mixture was diluted with ethyl acetate, and then the resulting precipitates were filtered off. The solvent was evaporated, and the resulting residue was purified by NH silica gel column chromatography (ethyl acetate/n-hexane system), to give 0.14 g of the free compound of the title compound as a colorless viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.15(t,J=7.2Hz,3H), 1.14-1.70(m,7H), 1.88-1.95(m,1H), 2.20-2.31(m,1H), 2.30(br-s,1H), 2.49(q,J=7.2Hz,2H), 2.66(t,J=5.0Hz,4H), 3.83(t,J=5.0Hz,4H), 4.44(d,J=8.4Hz,1H), 7.32(d,J=5.2Hz,1H), 7.41(d,J=8.4Hz,2H), 7.54(d,J=5.2Hz,1H), 7.64(s,1H), 8.05(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/IPE, to give the title compound as a yellow powder.

Hydrochloride:

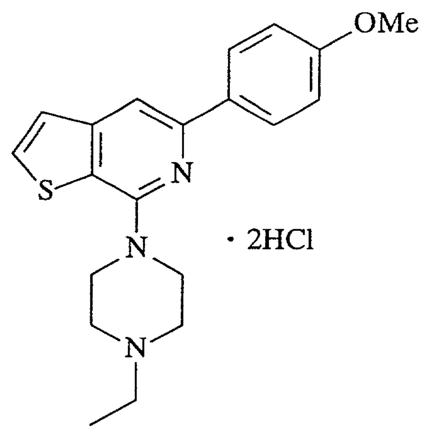
m.p.; 128-129°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.18-1.61(m,7H),

1.31(t,J=7.2Hz,3H), 1.65-1.72(m,1H), 2.07-2.17(m,1H), 3.16-3.24(m,4H), 3.55-3.66(m,4H), 4.34(d,J=7.6Hz,1H), 4.43(br-d,2H), 7.42(d,J=8.4Hz,2H), 7.57(d,J=5.2Hz,1H), 8.02(s,1H), 8.07(d,J=8.4Hz,2H), 8.07(d,J=5.2Hz,1H), 11.01(br-s,1H).

MS(FAB) m/z 422$(M+H)^+$.

Example 459 Synthesis of 7-(4-ethylpiperazin-1-yl)-5-(4-methoxyphenyl)thieno[2,3-c]pyridine dihydrochloride



A mixture of 5-bromo-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine (0.35 g), 4-methoxyphenylboric acid (0.24 g), tetrakistriphenylphosphinepalladium (0) (0.06 g), toluene (30 ml) and a 10% aqueous solution of sodium carbonate (20 ml) was vigorously stirred in nitrogen atmosphere at 100°C for 1 hr. To the resulting mixture was added 4-methoxyphenylboric acid (0.16 g), and the resulting mixture was further stirred for 2 hr. To the resulting mixture was added 4-methoxyphenylboric acid (0.16 g), and the resulting mixture was stirred for 6.5 hr. The resulting insoluble matters were filtered off, and then the organic layer was separated. It was extracted with 2N hydrochloric acid twice, adjusted to pH 10

by adding a 8N aqueous solution of sodium hydroxide thereto, and then extracted with ethyl acetate twice. After washing with brine and drying over magnesium sulfate, the solvent was evaporated. The resulting residue was purified by NH silica gel column chromatography (ethyl acetate/n-hexane system), to give 0.34 g of the free compound of the title compound as a pale yellow viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.15(t,J=7.2Hz,3H), 2.50(q,J=7.2Hz,2H), 2.67(t,J=5.0Hz,4H), 3.84(t,J=5.0Hz,4H), 3.85(s,3H), 6.98(d,J=9.0Hz,2H), 7.30(d,J=5.2Hz,1H), 7.51(d,J=5.2Hz,1H), 7.59(s,1H), 8.04(d,J=9.0Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a yellow powder.

Hydrochloride:

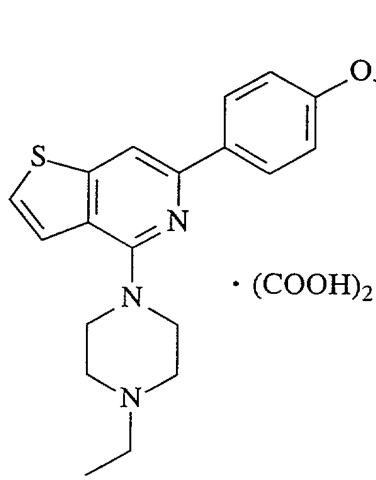
m.p.; 113-115°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.30(t,J=7.4Hz,3H), 3.16-3.24(m,4H), 3.53(br-t,2H), 3.65(br-d,2H), 3.82(s,3H), 4.43(br-d,2H), 7.05(d,J=8.8Hz,2H), 7.54(d,J=5.4Hz,1H), 7.97(s,1H), 8.06(d,J=5.4Hz,1H), 8.09(d,J=8.8Hz,2H), 10.64(br-s,1H).

MS(ESI) m/z 354(M+H)$^+$.

Example 460 Synthesis of 4-(4-ethylpiperazin-1-yl)-6-[4-(1,3-dioxolan-2-yl)methoxyphenyl]thieno[3,2-c]pyridine

oxalate



In the same manner as in Example 259, the free compound of 4-(4-ethylpiperazin-1-yl)-6-[4-(1,3-dioxolan-2-yl)methoxyphenyl]thieno[3,2-c]pyridine was obtained as a yellow viscous oil (1.60 g) from 2-bromo-3-thiophenecarboxyaldehyde (5.19 g) and 1-(1,3-dioxolan-2-yl)methoxy-4-ethynylbenzene (5.89 g).

Free compound:

^{1}H-NMR(400MHz, $CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 2.52(q,J=7.2Hz,2H), 2.69(br-t,4H), 3.70(br-t,4H), 3.96-4.02(m,2H), 4.04-4.12(m,2H), 4.10(d,J=4.0Hz,2H), 5.33(t,J=4.0Hz,1H), 7.02(d,J=9.2Hz,2H), 7.31(d,J=5.6Hz,1H), 7.39(dd,J=0.8,5.6Hz,1H), 7.72(d,J=0.8Hz,1H), 8.04(d,J=9.2Hz,2H).

The resulting free compound was converted into an oxalate in a conventional manner, and then recrystallized from methanol/ether, to give the title compound as a pale yellow powder.

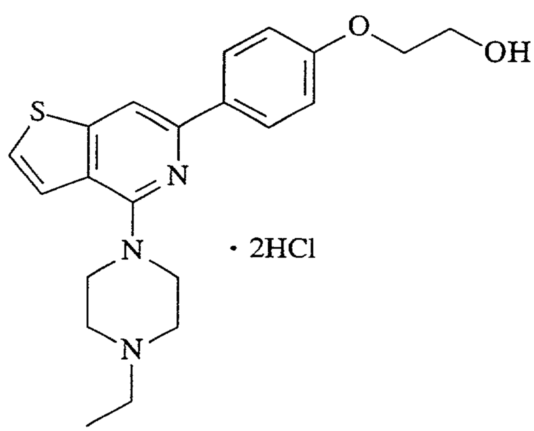
Oxalate:

m.p.; 188-189°C (decomp.)

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.24(t,J=7.2Hz,3H), 3.08(br-q,2H), 3.28(br-s,4H), 3.76(br-s,4H), 3.86-3.92(m,2H), 3.94-4.00(m,2H), 4.07(d,J=4.0Hz,2H), 5.23(J=4.0Hz,1H), 7.06(d,J=9.2Hz,2H), 7.60(d,J=5.6Hz,1H), 7.77(d,J=5.6Hz,1H), 8.10(d,J=9.2Hz,2H), 8.16(s,1H).

MS(ESI) m/z 416(M+H)$^+$.

<u>Example 461 Synthesis of 4-(4-Ethylpiperazin-1-yl)-6-[4-(2-hydroxyethoxy)phenyl]thieno[3,2-c]pyridine dihydrochloride</u>



4-(4-Ethylpiperazin-1-yl)-6-(4-hydroxyphenyl)thieno[3,2-c]pyridine (0.52 g) obtained by the method of Example 280 was treated in the same manner as in Example 417, to give 0.20 g of the free compound of the title compound as pale yellow prisms.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 2.09(br-s,1H), 2.53(q,J=7.2Hz,2H), 2.70(t,J=4.8Hz,4H), 3.70(t,J=4.8Hz,4H), 4.00(br-t,2H), 4.15(t,J=4.4Hz,2H),

7.00(d,J=9.0Hz,2H), 7.32(d,J=5.6Hz,1H), 7.39(dd,J=0.8,5.6Hz,1H), 7.72(d,J=0.8Hz,1H), 8.05(d,J=9.0Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a pale yellow powder.

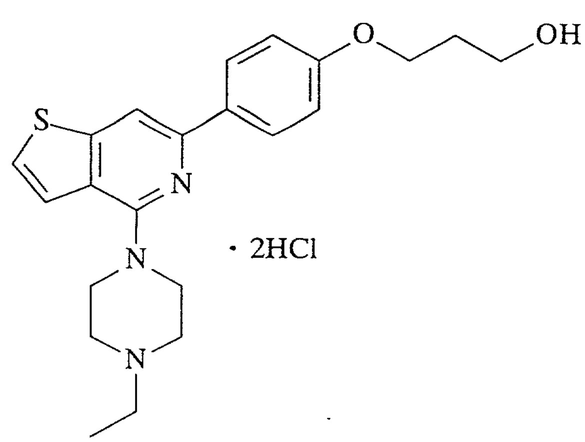
Hydrochloride:

m.p.; 128-129°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.31(t,J=7.2Hz,3H), 3.18-3.28(m,4H), 3.50(br-t,2H), 3.60(br-d,2H), 3.75(t,J=5.1Hz,2H), 4.05(t,J=5.1Hz,2H), 4.22(br-d,2H), 7.05(d,J=8.8Hz,2H), 7.62(d,J=7.2Hz,1H), 7.79(d,J=5.6Hz,1H), 8.10(d,J=8.8Hz,2H), 8.18(s,1H), 10.76(br-s,1H).

MS(ESI) m/z 384(M+H)$^{+}$.

Example 462 Synthesis of 4-(4-ethylpiperazin-1-yl)-6-[4-(3-hydroxypropoxy)phenyl]thieno[3,2-c]pyridine dihydrochloride



4-(4-Ethylpiperazin-1-yl)-6-(4-hydroxyphenyl)thieno[3,2-c]pyridine (0.40 g) obtained by the

method of Example 280 was treated in the same manner as in Example 417, to give 4-(4-ethylpiperazin-1-yl)-6-{4-[2-(3-tetrahydropyran-2-yl)oxypropoxy]phenyl}thieno[3,2-c]pyridine (0.47 g) as a pale yellow viscous oil.

Methanol (5 ml) and 2N hydrochloric acid (2 ml) were added to the resulting 4-(4-ethylpiperazin-1-yl)-6-{4-[2-(3-tetrahydropyran-2-yl)oxypropoxy]phenyl}thieno[3,2-c]pyridine (0.47 g), and the resulting mixture was stirred at room temperature. The solvent was evaporated, and then the pH of the resulting residue was adjusted to pH 10 by adding a 8N aqueous solution of sodium hydroxide thereto. The resulting solution was extracted with ethyl acetate, washed with brine and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.18 g of the free compound of the title compound as a pale yellow viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.15(t,J=7.2Hz,3H), 2.04(tt,J=6.0,6.0Hz,2H), 2.48-2.53(br-s,1H), 2.51(q,J=7.2Hz,2H), 2.68(t,J=4.9Hz,4H), 3.69(t,J=4.9Hz,4H), 3.85(t,J=6.0Hz,2H), 4.15(t,J=6.0Hz,2H), 6.96(d,J=9.0Hz,2H), 7.29(d,J=5.6Hz,1H), 7.36(dd,J=1.6,5.6Hz,1H), 7.69(d,J=1.6Hz,1H), 8.01(d,J=9.0Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated

with ethanol/ether, to give the title compound as a pale yellow powder.

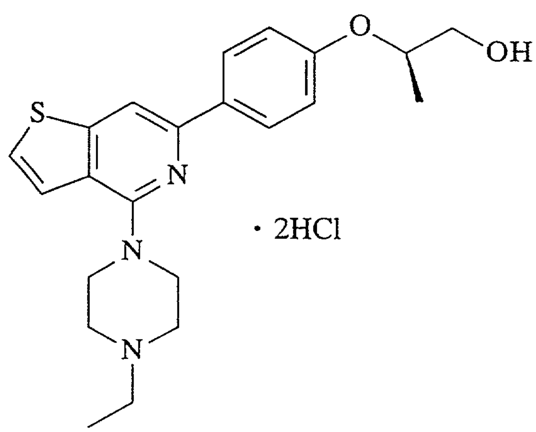
Hydrochloride:

m.p.; 102-104°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.31(t,J=7.2Hz,3H), 1.89(tt,J=6.2,6.2Hz,2H), 3.17-3.28(m,4H), 3.50(br-t,2H), 3.57-3.61(m,2H), 3.58(t,J=6.2Hz,2H), 4.10(t,J=6.2Hz,2H), 4.21(br-d,2H), 7.03(d,J=8.8Hz,2H), 7.61(d,J=5.6Hz,1H), 7.78(d,J=5.6Hz,1H), 8.10(d,J=5.6Hz,1H), 8.18(s,1H), 10.77(br-s,1H).

MS(ESI) m/z 398(M+H)$^+$.

Example 463 Synthesis of 4-(4-ethylpiperazin-1-yl)-6-[4-(2-hydroxy-1-methylethoxy)phenyl]thieno[3,2-c]pyridine dihydrochloride



4-(4-Ethylpiperazin-1-yl)-6-(4-hydroxyphenyl)thieno[3,2-c]pyridine (0.31 g) obtained by the method of Example 280 was treated in the same manner as in Example 464, to give 0.16 g of the free compound of the title compound as pale yellow prisms.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 1.32(d,J=6.4Hz,3H), 2.53(q,J=7.2Hz,2H), 2.71(t,J=5.0Hz,4H), 3.70(t,J=5.0Hz,4H), 3.75(dd,J=6.4,11.6Hz,1H), 3.80(dd,J=3.6,11.6Hz,1H), 4.54-4.61(m,1H), 7.01(d,J=8.8Hz,2H), 7.32(d,J=5.6Hz,1H), 7.39(dd,J=0.8,5.6Hz,1H), 7.72(d,J=0.8Hz,1H), 8.04(d,J=8.8Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a pale yellow powder.

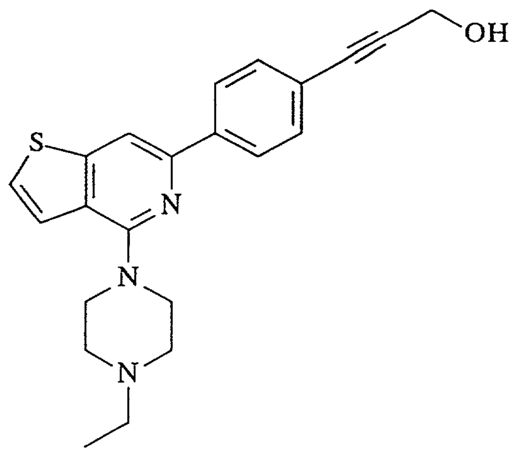
Hydrochloride:

m.p.; 124-125°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.24(d,J=6.0Hz,3H), 1.30(t,J=7.2Hz,3H), 3.18-3.37(m,4H), 3.44-3.51(m,3H), 3.56-3.61(m,3H), 4.22(br-d,2H), 4.48-4.54(m,1H), 7.04(d,J=9.0Hz,2H), 7.62(d,J=5.6Hz,1H), 7.79(d,J=5.6Hz,1H), 8.08(d,J=9.0Hz,2H), 8.17(s,1H), 10.56(br-s,1H).

MS(FAB) m/z 398$(M+H)^+$.

Example 464 Synthesis of 4-(4-ethylpiperazin-1-yl)-6-[4-(3-hydroxy-1-propynyl)phenyl]thieno[3,2-c]pyridine pyridine



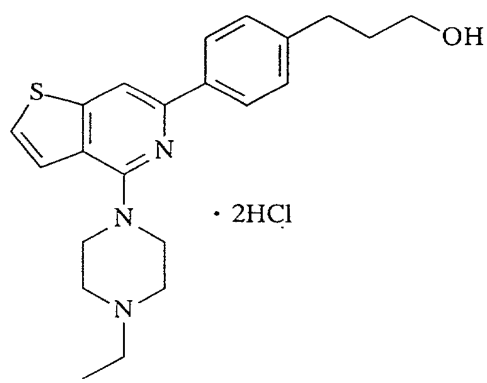
In the same manner as in Example 281-3, 6-(4-bromophenyl)-4-(4-ethylpiperazin-1-yl)thieno[3,2-c]pyridine (1.27 g) and propargyl alcohol (0.92 ml) were reacted, and then recrystallized from chloroform/n-hexane, to give 0.41 g of the title compound as pale yellow needles.

m.p.; 149-5-150.5°C (decomp.)

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.53(q,J=7.2Hz,2H), 2.70(t,J=5.0Hz,4H), 3.71(t,J=5.0Hz,4H), 4.53(s,2H), 7.37(d,J=5.6Hz,1H), 7.42(dd,J=0.8,5.6Hz,1H), 7.52(d,J=8.4Hz,2H), 7.80(d,J=0.8Hz,1H), 8.06(d,J=8.4Hz,2H).

MS(ESI) m/z 378(M+H)$^+$.

Example 465 Synthesis of 4-(4-ethylpiperazin-1-yl)-6-[4-(3-hydroxypropyl)phenyl]thieno[3,2-c]pyridine dihydrochloride



4-(4-Ethylpiperazin-1-yl)-6-[4-(3-hydroxy-1-propynyl)phenyl]thieno[3,2-c]pyridine (0.30 g) obtained in the previous Example was reduced in the same manner as in Example 291, to give 0.10 g of the free compound of the title compound.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.4Hz,3H), 1.89-1.96(m,2H), 2.52(q,J=7.4Hz,2H), 2.69(t,J=4.8Hz,4H), 2.76(t,J=7.6Hz,2H), 3.68-3.71(m,6H), 7.28(d,J=8.6Hz,2H), 7.33(d,J=5.6Hz,1H), 7.40(dd,J=0.8,5.6Hz,1H), 7.76(d,J=0.8Hz,1H), 8.02(d,J=8.6Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a colorless powder.

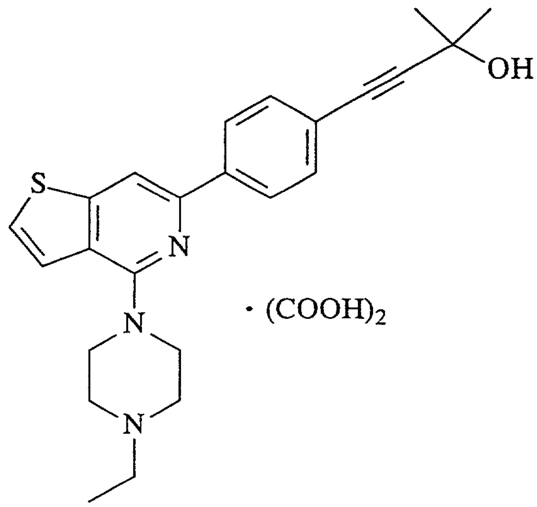
Hydrochloride:

m.p.; 125.5-126.5°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.30(t,J=7.2Hz,3H), 1.72-1.79(m,2H), 2.67(t,J=7.6Hz,2H), 3.18-3.29(m,4H), 3.44(t,J=6.4Hz,2H), 3.48(br-t,2H), 3.61(br-d,2H), 4.23(br-d,2H), 7.31(d,J=8.4Hz,2H), 7.64(d,J=5.6Hz,1H), 7.82(d,J=5.6Hz,1H), 8.06(d,J=8.4Hz,2H), 8.23(s,1H), 10.51(br-s,1H).

MS(ESI) m/z 382$(M+H)^+$.

<u>Example 466 Synthesis of 4-(4-ethylpiperazin-1-yl)-6-[4-(3-hydroxy-3-methyl-1-butynyl)phenyl]thieno[3,2-c]pyridine oxalate</u>



In the same manner as in Example 281-3, 6-(4-bromophenyl)-4-(4-ethylpiperazin-1-yl)thieno[3,2-c]pyridine (0.50 g) was reacted with 2-methyl-3-butyn-2-ol (0.16 ml), to give 0.28 g of the free compound of the title compound as a pale brown amorphous.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 1.65(s,6H), 2.53(q,J=7.2Hz,2H), 2.70(t,J=5.0Hz,4H), 3.71(t,J=5.0Hz,4H), 7.37(d,J=5.4Hz,1H), 7.41(dd,J=0.8,5.4Hz,1H), 7.49(d,J=8.2Hz,2H), 7.80(d,J=0.8Hz,1H), 8.05(d,J=8.2Hz,2H).

The resulting free compound was converted into an oxalate in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a colorless powder.

Oxalate:

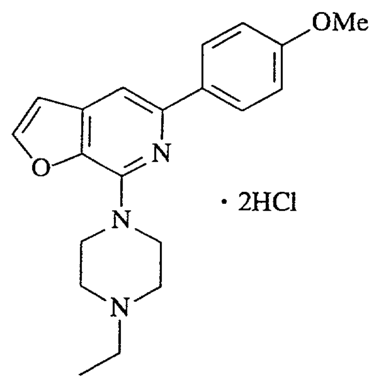
m.p.; 124.5-125.5°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.24(t,J=7.2Hz,3H), 1.49(s,6H), 3.08(br-q,2H), 3.29(br-t,4H), 3.78(br-t,4H), 7.49(d,J=8.4Hz,2H), 7.64(d,J=5.4Hz,1H), 7.85(d,J=5.4Hz,1H),

8.17(d,J=8.4Hz,2H), 8.29(s,1H).

MS(ESI) m/z 406$(M+H)^+$.

Example 467 Synthesis of 7-(4-ethylpiperazin-1-yl)-5-(4-methoxyphenyl)furo[2,3-c]pyridine dihydrochloride



A mixture of 5-bromo-7-(4-ethylpiperazin-1-yl)furo[2,3-c]pyridine (0.34 g), 4-methoxyphenylboric acid (0.25 g), tetrakistriphenylphosphinepalladium(0) (0.06 g), toluene (30 ml) and a 10% aqueous solution of sodium bicarbonate (20 ml) was vigorously stirred in nitrogen atmosphere at 100°C for 1 hr. To the mixture was then additionally added 4-methoxyphenylboric acid (0.17 g), and the resulting mixture was further stirred overnight. The insoluble matters were filtered off, and the organic layer was separated. Then, it was extracted twice with 2N hydrochloric acid, adjusted to pH 10 by adding a 8N aqueous solution of sodium hydroxide thereto, and then extracted with ethyl acetate twice. It was washed with brine, dried over magnesium sulfate, and then the solvent was evaporated. The resulting residue was purified by NH silica gel column chromatography (ethyl acetate/n-hexane system), to give 0.31 g of the free compound of the title compound as a pale

yellow viscous oil.

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 2.50(q,J=7.2Hz,2H), 2.65(t,J=5.0Hz,4H), 3.86(s,3H), 3.99(t,J=5.0Hz,4H), 6.73(d,J=2.2Hz,1H), 6.97(d,J=9.0Hz,2H), 7.32(s,1H), 7.61(d,J=2.2Hz,1H), 7.97(d,J=9.0Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then reprecipitated with ethanol/ether, to give the title compound as a yellow powder.

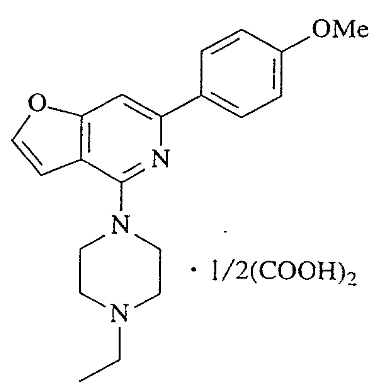
Hydrochloride:

m.p.; 127-128°C

^{1}H-NMR(400MHz,DMSO-d_6); δ (ppm) 1.29(t,J=7.2Hz,3H), 3.10-3.20(m,4H), 3.55(br-t,2H), 3.62(br-d,2H), 3.81(s,3H), 4.75(br-d,2H), 7.01(d,J=9.0Hz,2H), 7.02(d,J=1.8Hz,1H), 7.63(s,1H), 8.01(d,J=9.0Hz,2H), 8.14(d,J=1.8Hz,1H), 10.84(br-s,1H).

MS(ESI) m/z 338$(M+H)^+$.

Example 468 Synthesis of 4-(4-ethylpiperazin-1-yl)-6-(4-methoxyphenyl)furo[3,2-c]pyridine oxalate



In the same manner as in Example 259, the free compound of the title compound was obtained as a brown viscous oil (0.29 g) from 2-bromo-3-furancarboxyaldehyde (5.79 g) and 4-ethynylanisole (8.74 g).

Free compound:

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.16(t,J=7.2Hz,3H), 2.50(q,J=7.2Hz,2H), 2.65(t,J=5.0Hz,4H), 3.86(t,J=5.0Hz,4H), 3.86(s,3H), 6.81(dd,J=0.8,2.4Hz,1H), 6.97(d,J=9.0Hz,2H), 7.31(d,J=0.8Hz,1H), 7.51(d,J=2.4Hz,1H), 8.01(d,J=9.0Hz,2H).

The resulting free compound was converted into an oxalate in a conventional manner, and then reprecipitated with methanol/ether, to give the title compound as a pale yellow powder.

1/2 Oxalate:

m.p.; 170-172°C (decomp.)

^{1}H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.21(t,J=7.2Hz,3H), 2.96(br-q,2H), 3.13(br-s,4H), 3.81(s,3H), 3.92(br-s,4H), 7.02(d,J=8.8Hz,2H), 7.22(d,J=2.0Hz,1H), 7.64(s,1H), 7.98(d,J=2.0Hz,1H), 8.08(d,J=8.8Hz,2H).

MS(FAB) m/z 338$(M+H)^+$.